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=> file biosis, medline, embase, uspatfull, wpids

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COPYRIGHT (C) 1998 DERWENT INFORMATION LTD

=> s hmg-coa

L1         8321 HMG-COA

=> s hmg-coa reductase inhibitor###

L2         3111 HMG-COA REDUCTASE INHIBITOR###

=> s (lovastatin or pravastatin or simvastatin or fluvastatin or dalvastatin
or compactin)

L3        12172 (LOVASTATIN OR PRAVASTATIN OR SIMVASTATIN OR FLUVASTATIN
                OR DALVASTATIN OR COMPACTIN)

=> s l2 or l3

L4        13086 L2 OR L3

=> s arginine

L5       139344 ARGININE

=> s l5 and l4

L6          265 L5 AND L4

=> s vasodilat##### or vasorelax#######

L7       123146 VASODILAT##### OR VASORELAX#######

=> s l7 and l6

L8           26 L7 AND L6
```

=> s l2 and l5

L9 141 L2 AND L5

=> s l7 and l9

L10 2 L7 AND L9

=> s l8 not l10

L11 24 L8 NOT L10

=> d l10 1-2 bib,ab

L10 ANSWER 1 OF 2 USPATFULL
AN 97:98743 USPATFULL
TI Coronary vasculature treatment method
IN Igo, Stephen R., Clear Lake Shores, TX, United States
Meador, James W., Houston, TX, United States
PA Cormedics Corp., Clear Lake Shores, TX, United States (U.S. corporation)
PI US 5681278 971028
AI US 94-264458 940623 (8)
DT Utility
EXNAM Primary Examiner: McDermott, Corrine M.; Assistant Examiner: Smith, Chalin
LREP Burgess, Tim L.
CLMN Number of Claims: 21
ECL Exemplary Claim: 1
DRWN 24 Drawing Figure(s); 15 Drawing Page(s)
LN.CNT 1203
AB Method and apparatus for treating blood vessels in a mammal, particularly humans, especially coronary blood vessels, for vascular thrombosis and angioplasty restenosis, thereby to decrease incidence of vessel rethrombosis, unstable angina and myocardial infarction, by administering a conager of an endothelium-derived bioactive agent, especially a nitrovasodilator, including one or more of nitric oxide or a nitric oxide donor agent, such as sodium nitroprusside and nitroglycerin, to an extravascular treatment site at a therapeutically effective dosage rate.

L10 ANSWER 2 OF 2 USPATFULL
AN 97:46815 USPATFULL
TI Apparatus and method for transpericardial delivery of fluid
IN Igo, Stephen R., Clear Lake Shores, TX, United States
Meador, James W., Houston, TX, United States
PA Cormedics Corp., Clear Lake Shores, TX, United States (U.S. corporation)
PI US 5634895 970603
AI US 95-486104 950607 (8)
RLI Division of Ser. No. US 94-264458, filed on 23 Jun 1994
DT Utility
EXNAM Primary Examiner: McDermott, Corrine M.; Assistant Examiner: Smith, Chalin
LREP Burgess, Tim L.
CLMN Number of Claims: 23
ECL Exemplary Claim: 1
DRWN 24 Drawing Figure(s); 15 Drawing Page(s)
LN.CNT 1167
AB Method and apparatus for treating blood vessels in a mammal,

particularly humans, especially coronary blood vessels, for vascular thrombosis and angioplasty restenosis, thereby to decrease incidence of vessel rethrombosis, unstable angina and myocardial infarction, by administering a conager of an endothelium-derived bioactive agent, especially a nitrovasodilator, including one or more of nitric oxide or a nitric oxide donor agent, such as sodium nitroprusside and nitroglycerin, to an extravascular treatment site at a therapeutically effective dosage rate.

=> d his

(FILE 'HOME' ENTERED AT 17:22:19 ON 28 JAN 1998)

FILE 'BIOSIS, MEDLINE, EMBASE, USPATFULL, WPIDS' ENTERED AT 17:25:03 ON 28 JAN 1998

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L1          8321 S HMG-COA
L2          3111 S HMG-COA REDUCTASE INHIBITOR###
L3         12172 S (LOVASTATIN OR PRAVASTATIN OR SIMVASTATIN OR FLUVASTATI
L4         13086 S L2 OR L3
L5        139344 S ARGININE
L6           265 S L5 AND L4
L7        123146 S VASODILAT##### OR VASORELAX#######
L8            26 S L7 AND L6
L9           141 S L2 AND L5
L10            2 S L7 AND L9
L11           24 S L8 NOT L10
```

=> d l11 1-24 bib,ab

L11 ANSWER 1 OF 24 BIOSIS COPYRIGHT 1998 BIOSIS
AN 97:478718 BIOSIS
DN 99777921
TI Lowering of LDL-cholesterol improves endothelial function of the forearm vasculature: A placebo-controlled study.
AU John S; Schlaich M P; Langenfeld M R W; Weihprecht H; Schmitz G; Schmieder R E
CS Dep. Med. IV, Univ. Erlangen-Nuremberg, Erlangen, Germany
SO XIXth Congress of the European Society of Cardiology together with the 32nd Annual General Meeting of the Association of European Paediatric Cardiologists (AEPC), Stockholm, Sweden, August 24-28, 1997. European Heart Journal 18 (ABSTR. SUPPL.). 1997. 34. ISSN: 0195-668X
DT Conference
LA English

L11 ANSWER 2 OF 24 BIOSIS COPYRIGHT 1998 BIOSIS
AN 97:411182 BIOSIS
DN 99703225
TI Dietary L-**arginine** reduces the progression of atherosclerosis in cholesterol-fed rabbits: Comparison with **lovastatin**.
AU Boeger R H; Bode-Boeger S M; Brandes R P; Phivthong-Ngam L; Boehme M; Nafe R; Muegge A; Froelich J C
CS Inst. Clinical Pharmacol., Hannover Med. Sch., Konstanty-Gutschow-Str. 8, 30625 Hannover, Germany
SO Circulation 96 (4). 1997. 1282-1290. ISSN: 0009-7322
LA English
AB Background. We investigated whether L-**arginine** induces regression of preexisting atheromatous lesions and reversal of endothelial dysfunction in hypercholesterolemic rabbits, whether

similar effects can be obtained by cholesterol-lowering therapy with **lovastatin**, and which mechanism leads to these effects. Methods and Results. Rabbits were fed 1% cholesterol for 4 weeks and 0.5% cholesterol for an additional 12 weeks. Two groups of cholesterol-fed rabbits were treated with L-**arginine** (2.0% in drinking water) or **lovastatin** (10 mg/d) during weeks 5 through 16. Systemic nitric oxide (NO) formation was assessed as the urinary excretion rates of nitrate and cGMP in weekly intervals. Cholesterol feeding progressively reduced urinary nitrate excretion to apprxeq 40% of baseline (P lt .05) and increased plasma concentrations of asymmetrical dimethylarginine (ADMA), an endogenous NO synthesis inhibitor. Dietary L-**arginine** reversed the reduction in plasma L-**arginine**/ADMA ratio and partly restored urinary excretion of nitrate and cGMP (each P lt .05 vs cholesterol) but did not change plasma cholesterol levels. L-**Arginine** completely blocked the progression of carotid intimal Plaques, reduced aortic intimal thickening, and preserved endothelium-dependent **vasodilator** function. **Lovastatin** treatment reduced plasma cholesterol by 32% but did not improve urinary nitrate or cGMP excretion or endothelium-dependent **vasodilation**. **Lovastatin** had a weaker inhibitory effect on carotid plaque formation and aortic intimal thickening than L-**arginine**. L-**Arginine** inhibited but **lovastatin** potentiated superoxide radical generation in the atherosclerotic vascular wall. Conclusions. Dietary L-**arginine** improves NO-dependent **vasodilator** function in cholesterol-fed rabbits and completely blocks the progression of plaques via restoration of NO synthase substrate availability and reduction of vascular oxidative stress. **Lovastatin** treatment has a weaker inhibitory effect on the progression of atherosclerosis and no effect on vascular NO elaboration, which may be due to its stimulatory effect on vascular superoxide radical generation.

L11 ANSWER 3 OF 24 BIOSIS COPYRIGHT 1998 BIOSIS
AN 97:161833 BIOSIS
DN 99461036
TI **Simvastatin**, an HMG-coenzyme A reductase inhibitor, improves endothelial function within 1 month.
AU O'Driscoll G; Green D; Taylor R R
CS Dep. Cardiol., Royal Perth Hosp., Wellington St., Perth 6000, Western Australia
SO Circulation 95 (5). 1997. 1126-1131. ISSN: 0009-7322
LA English
AB Background. Cholesterol-lowering therapy can improve cardiovascular morbidity and mortality in patients with atherosclerosis. Although the mechanisms responsible are unclear, these benefits precede macroscopic changes in the vasculature. Emerging evidence that improvement in endothelial function may occur requires substantiation; in particular, it is unclear how early any such improvement would be detectable after initiation of therapy. Methods and Results. This randomized, double-blind, placebo-controlled crossover study evaluated the effect of **simvastatin** (20 mg daily for 4 weeks) on endothelium-dependent and endothelium-independent **vasodilation** and on the response to the inhibitor of nitric oxide synthesis, N-G-monomethyl-L-**arginine** (L-NMMA), in the forearm vasculature of subjects with moderate elevation of total serum cholesterol (6.0 to 10.0 mmol/L) by use of strain-gauge plethysmography. Studies were repeated after 3 more months of open therapy. When the results are expressed as percentage changes in flow in the infused arm relative to the noninfused arm, the **vasodilator** response to acetylcholine was significantly increased after 4 weeks of treatment with

simvastatin (P lt .0005), and this improvement was further enhanced after 3 months (P lt .005). Concurrently, **simvastatin** augmented the vasoconstrictor response to L-NMMA, an effect that was maintained at 3 months (P lt .0005). The response to the endothelium-independent **vasodilator** sodium nitroprusside was unaltered. Conclusions. These observations indicate that within 1 month of treatment with **simvastatin**, both the stimulated and basal nitric oxide dilator functions of the endothelium are augmented, and the benefits of this HMG-coenzyme A reductase inhibitor persist with continued therapy.

L11 ANSWER 4 OF 24 BIOSIS COPYRIGHT 1998 BIOSIS
AN 96:454536 BIOSIS
DN 99176892
TI L-**arginine** improves endothelial **vasodilator** function and slows the progression, but does not induce regression of atherosclerosis in cholesterol-fed rabbits: Comparison with **lovastatin**.
AU Phivthong-Ngam L; Bode-Boeger S M; Boeger R H; Boehme M; Brandes R P; Muegge A; Froelich J C
CS Inst. Clin. Pharmacol., Med. Sch., D-30623 Hannover, Germany
SO 6th Annual Meeting of the German Society for Clinical Pharmacology and Therapeutics, Dresden, Germany, September 5-7, 1996. European Journal of Clinical Pharmacology 50 (6). 1996. 551. ISSN: 0031-6970
DT Conference
LA English

L11 ANSWER 5 OF 24 BIOSIS COPYRIGHT 1998 BIOSIS
AN 96:210279 BIOSIS
DN 98766408
TI **Lovastatin** enhances the renal microvascular **vasodilator** response to acetylcholine.
AU Inman S R; Stowe N T; Novick A C
CS Cleveland Clin. Found., Cleveland, OH 44195, USA
SO Experimental Biology 96, Part II, Washington, D.C., USA, April 14-17, 1996. FASEB Journal 10 (3). 1996. A547. ISSN: 0892-6638
DT Conference
LA English

L11 ANSWER 6 OF 24 BIOSIS COPYRIGHT 1998 BIOSIS
AN 95:458482 BIOSIS
DN 98472782
TI Vascular function in the forearm of hypercholesterolaemic patients off and on lipid-lowering medication.
AU Stroes E S G; Koomans H A; De Bruin T W A; Rabelink T J
CS Dep. Nephrol. Hypertension, Room F03.226, Heidelberglaan 100, 3584 CX, Netherlands
SO Lancet (North American Edition) 346 (8973). 1995. 467-471. ISSN: 0099-5355
LA English
AB To study whether vascular dysfunction in hypercholesterolaemia is reversible, we investigated patients without overt arterial disease who were taking maintenance treatment for hypercholesterolaemia. Medication was stopped for 2 weeks, reinstituted for 12 weeks, and again stopped for 6 weeks. During both maintenance treatment and the 12 weeks of step-up medication the lipid profile was improved but did not return to normal. Dose-response curves for serotonin-induced **vasodilatation**, an index of nitric oxide-dependent **vasodilatation**, showed a comparable and significant rightward shift after a medication-free period of 2 and 6 weeks compared with control subjects, indicating endothelial dysfunction, which was already maximum after 2 weeks. After 12 weeks of lipid-lowering medication, the difference in endothelial function between controls

and patients had disappeared. Co-infusion of L-**arginine**, the substrate for nitric oxide synthase, returned the impaired serotonin response during hypercholesterolaemia to normal, but had no effect on this response in, controls or in patients while on lipid-lowering medication. Neither endothelium-independent **vasorelaxation**, assessed by sodium nitroprusside infusion, nor vasoconstriction induced by the nitric Oxide blocker L-NMMA, were different between controls and patients, whether the latter were on or off lipid-lowering medication. Our results show an L-**arginine**-sensitive, impaired nitricoxide-mediated vascular relaxation of forearm resistance vessels in hypercholesterolaemia which is reproducible, and reversible after short-term lipid-lowering therapy. Demonstration of such changes in this readily accessible vascular bed will allow larger trials assessing vascular function during lipid-lowering therapy to be done.

L11 ANSWER 7 OF 24 BIOSIS COPYRIGHT 1998 BIOSIS
AN 95:30939 BIOSIS
DN 98045239
TI The effect of probucol and vitamin E treatment on the oxidation of low-density lipoprotein and forearm vascular responses in humans.
AU McDowell I F W; Brennan G M; McEneny J; Young I S; Nicholls D P; McVeigh G E; Bruce I; Trimble E R; Johnston G D
CS Dep. Med. Biochem., Univ. Wales Coll. Med., Cardiff CF4 4XN, UK
SO European Journal of Clinical Investigation 24 (11). 1994. 759-765. ISSN: 0014-2972
LA English
AB This study investigates the hypothesis that lipid soluble antioxidants may increase the resistance of low-density lipoprotein (LDL) to oxidation and also enhance vascular endothelial responses in humans. In a double-blind parallel group study, 24 hypercholesterolaemic patients, already on treatment with **simvastatin** (20 mg day-1), were randomized to supplementary treatment with probucol (500 mg bd), vitamin E (400 IU daily) or placebo for 8 weeks. Mean serum cholesterol before antioxidant treatment was 7.00 mmol l-1. Resistance of LDL to oxidation by copper was increased by 830% in the probucol group and by 30% in the vitamin E group. However, thiobarbituric acid reacting substances in whole serum were not altered by either antioxidant. Probucol lowered HDL- and LDL-cholesterol levels and increased the QT interval. Forearm vascular responses, as measured by venous occlusion plethysmography, to acetylcholine, glyceryl trinitrate and NG-monomethyl-L-**arginine**, were not significantly changed by antioxidant treatment. Probucol has a major, and vitamin E a minor, effect on LDL resistance to oxidation but neither compound appears to alter forearm vascular responses in vivo.

L11 ANSWER 8 OF 24 BIOSIS COPYRIGHT 1998 BIOSIS
AN 92:69063 BIOSIS
DN BA93:37518
TI HYPERCHOLESTEROLEMIA AND ATHEROSCLEROSIS CHANGE VASCULAR REACTIVITY IN RABBITS BY DIFFERENT MECHANISMS.
AU GALLE J; BUSSE R; BASSENGE E
CS INSTITUT FUER ANGEWANDTE PHYSIOLOGIE DER UNIVERSITAET, HERMANN HERDER STRASSE 7, D-7800 FREIBURG, WEST GERMANY.
SO ARTERIOSCLER THROMB 11 (6). 1991. 1712-1718. CODEN: ARTTE5 ISSN: 1049-8834
LA English
AB Vasomotor reactivity was assessed in vitro in arterial segments obtained from rabbits with different stages of atherosclerosis. Rabbits were fed a standard chow diet (controls) or a cholesterol-enriched diet to induce hypercholesterolemia and atherosclerosis. A third group received the hydroxymethylglutaryl

coenzyme A reductase inhibitor, **lovastatin**, simultaneously with the cholesterol diet. Contractile responses of thoracic aortas to norepinephrine, serotonin, and potassium-rich solution, as well as endothelium-dependent dilations to acetylcholine, were compared after 2 and 4 months on the respective diet. Additionally, plasma cholesterol levels and the amount of plaques covering the intimal surface (as a percentage of the intimal surface) were determined; transmission electron microscopy of atherosclerotic arteries was also performed. After 2 months, the only difference was an enhancement of contractile responses to serotonin in the cholesterol-fed versus the control group. After 4 months on the diet, contractile responses to serotonin were further enhanced, and norepinephrine- and potassium-induced vasoconstrictions were now also significantly enhanced in cholesterol-fed animals versus controls. Endothelium-dependent **vasodilations** were simultaneously reduced in cholesterol-fed animals. These alterations were partly prevented in cholesterol-fed and **lovastatin**-treated animals. Suppression of nitric oxide synthesis in control aortas by NG-nitro-L-**arginine** did not reveal any significant increases in contractile responses. Contractile responses to serotonin were enhanced after 2 months on the diet but before the appearance of intimal plaques, whereas attenuation of endothelium-dependent dilations, as well as the further enhancement of contractile responses to serotonin and to other agonists, were closely correlated with the degree of intimal plaques after 4 months on the diet. The similarity of alterations in vascular reactivity after 4 months on the diet to the effects of isolated low density lipoproteins on vascular tone and the correlation of these changes with the degree of lipid-containing plaques support the hypothesis that lipoprotein accumulation in atheroclerotic arteries contributes to alterd vascular reactivity.

L11 ANSWER 9 OF 24 MEDLINE
AN 97431455 MEDLINE
DN 97431455
TI Dietary L-**arginine** reduces the progression of atherosclerosis in cholesterol-fed rabbits: comparison with **lovastatin**.
AU Boger R H; Bode-Boger S M; Brandes R P; Phivthong-ngam L; Bohme M; Nafe R; Mugge A; Frolich J C
CS Institute of Clinical Pharmacology, Medical School, Hannover, Germany.
SO CIRCULATION, (1997 Aug 19) 96 (4) 1282-90.
Journal code: DAW. ISSN: 0009-7322.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199711
EW 19971104
AB BACKGROUND: We investigated whether L-**arginine** induces regression of preexisting atheromatous lesions and reversal of endothelial dysfunction in hypercholesterolemic rabbits, whether similar effects can be obtained by cholesterol-lowering therapy with **lovastatin**, and which mechanism leads to these effects. METHODS AND RESULTS: Rabbits were fed 1% cholesterol for 4 weeks and 0.5% cholesterol for an additional 12 weeks. Two groups of cholesterol-fed rabbits were treated with L-**arginine** (2.0% in drinking water) or **lovastatin** (10 mg/d) during weeks 5 through 16. Systemic nitric oxide (NO) formation was assessed as the urinary excretion rates of nitrate and cGMP in weekly intervals. Cholesterol feeding progressively reduced urinary nitrate excretion to approximately 40% of baseline ($P<.05$) and increased plasma

concentrations of asymmetrical dimethylarginine (ADMA), an endogenous NO synthesis inhibitor. Dietary L-**arginine** reversed the reduction in plasma L-**arginine**/ADMA ratio and partly restored urinary excretion of nitrate and cGMP (each P<.05 vs cholesterol) but did not change plasma cholesterol levels. L-**Arginine** completely blocked the progression of carotid intimal plaques, reduced aortic intimal thickening, and preserved endothelium-dependent **vasodilator** function. **Lovastatin** treatment reduced plasma cholesterol by 32% but did not improve urinary nitrate or cGMP excretion or endothelium-dependent **vasodilation**. **Lovastatin** had a weaker inhibitory effect on carotid plaque formation and aortic intimal thickening than L-**arginine**. L-**Arginine** inhibited but **lovastatin** potentiated superoxide radical generation in the atherosclerotic vascular wall. CONCLUSIONS: Dietary L-**arginine** improves NO-dependent **vasodilator** function in cholesterol-fed rabbits and completely blocks the progression of plaques via restoration of NO synthase substrate availability and reduction of vascular oxidative stress. **Lovastatin** treatment has a weaker inhibitory effect on the progression of atherosclerosis and no effect on vascular NO elaboration, which may be due to its stimulatory effect on vascular superoxide radical generation.

L11 ANSWER 10 OF 24 MEDLINE
AN 97207547 MEDLINE
DN 97207547
TI **Simvastatin**, an HMG-~~coenzyme A~~ reductase inhibitor, improves endothelial function within 1 month.
AU O'Driscoll G; Green D; Taylor R R
CS Department of Cardiology and Medicine, Royal Perth (Australia) Hospital.
SO CIRCULATION, (1997 Mar 4) 95 (5) 1126-31.
Journal code: DAW. ISSN: 0009-7322.
CY United States
DT (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199706
EW 19970601
AB BACKGROUND: Cholesterol-lowering therapy can improve cardiovascular morbidity and mortality in patients with atherosclerosis. Although the mechanisms responsible are unclear, these benefits precede macroscopic changes in the vasculature. Emerging evidence that improvement in endothelial function may occur requires substantiation; in particular, it is unclear how early any such improvement would be detectable after initiation of therapy. METHODS AND RESULTS: This randomized, double-blind, placebo-controlled crossover study evaluated the effect of **simvastatin** (20 mg daily for 4 weeks) on endothelium-dependent and endothelium-independent **vasodilation** and on the response to the inhibitor of nitric oxide synthesis, NG-monomethyl-L-**arginine** (L-NMMA), in the forearm vasculature of subjects with moderate elevation of total serum cholesterol (6.0 to 10.0 mmol/L) by use of strain-gauge plethysmography. Studies were repeated after 3 more months of open therapy. When the results are expressed as percentage changes in flow in the infused arm relative to the noninfused arm, the **vasodilator** response to acetylcholine was significantly increased after 4 weeks of treatment with **simvastatin** ($P < .0005$), and this improvement was further enhanced after 3 months ($P < .005$). Concurrently,

simvastatin augmented the vasoconstrictor response to L-NMMA, an effect that was maintained at 3 months ($P < .0005$). The response to the endothelium-independent **vasodilator** sodium nitroprusside was unaltered. CONCLUSIONS: These observations indicate that within 1 month of treatment with **simvastatin**, both the stimulated and basal nitric oxide dilator functions of the endothelium are augmented, and the benefits of this HMG-coenzyme A reductase inhibitor persist with continued therapy.

L11 ANSWER 11 OF 24 MEDLINE
AN 97020373 MEDLINE
DN 97020373
TI Preservation of endothelium-dependent vascular relaxation in cholesterol-fed mice by the chronic administration of prazosin or **pravastatin**.
AU Kamata K; Kojima S; Sugiura M; Kasuya Y
CS Department of Physiology and Morphology, Hoshi University, Tokyo, Japan.
SO JAPANESE JOURNAL OF PHARMACOLOGY, (1996 Feb) 70 (2) 149-56.
Journal code: KO7. ISSN: 0021-5198.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199702
EW 19970204
AB The relaxation of aortic rings in response to acetylcholine (ACh) was significantly decreased in cholesterol-fed mice. The attenuated relaxation in cholesterol-fed mice was preserved by the chronic administration of prazosin (20 mg/kg/day) or **pravastatin** (12.5 mg/kg/day). Serum low-density lipoprotein (LDL) levels were significantly increased in mice given cholesterol. The increased serum LDL levels in cholesterol-fed mice were returned to normal by the chronic administration of prazosin and **pravastatin**. A prior incubation of aortic rings with lysophosphatidylcholine (LPC) significantly attenuated ACh- and A23187-induced endothelium-dependent relaxation. The inhibitory effects of LPC on endothelium-dependent relaxation were not affected by indomethacin or superoxide dismutase. The sodium nitroprusside-induced relaxation of aortic rings was not changed by LPC. The inhibitory effects on ACh-induced relaxation by NG-monomethyl-L-**arginine** were restored by a prior exposure to L-**arginine**, whereas the inhibition of endothelium-dependent relaxation by LPC was not affected by L-**arginine**. These results suggest that cholesterol-fed mice are useful animal models of hypercholesterolemia, and chronic administration of prazosin or **pravastatin** can preserve endothelium-dependent relaxation by lowering serum LDL in these animals. It is further suggested that LPC derived from oxidized LDL may be involved in the reduced endothelium-dependent relaxation in hyperlipidemia.

L11 ANSWER 12 OF 24 MEDLINE
AN 95364506 MEDLINE
DN 95364506
TI Vascular function in the forearm of hypercholesterolaemic patients off and on lipid-lowering medication.
AU Stroes E S; Koomans H A; de Bruin T W; Rabelink T J
CS Department of Nephrology, University Hospital Utrecht, The Netherlands.
SO LANCET, (1995 Aug 19) 346 (8973) 467-71.
Journal code: L0S. ISSN: 0140-6736.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)

LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199511
AB To study whether vascular dysfunction in hypercholesterolaemia is reversible, we investigated patients without overt arterial disease who were taking maintenance treatment for hypercholesterolaemia. Medication was stopped for 2 weeks, reinstituted for 12 weeks, and again stopped for 6 weeks. During both maintenance treatment and the 12 weeks of step-up medication the lipid profile was improved but did not return to normal. Dose-response curves for serotonin-induced **vasodilatation**, an index of nitric oxide-dependent **vasodilatation**, showed a comparable and significant rightward shift after a medication-free period of 2 and 6 weeks compared with control subjects, indicating endothelial dysfunction, which was already maximum after 2 weeks. After 12 weeks of lipid-lowering medication, the difference in endothelial function between controls and patients had disappeared. Co-infusion of L-**arginine**, the substrate for nitric oxide synthase, returned the impaired serotonin response during hypercholesterolaemia to normal, but had no effect on this response in controls or in patients while on lipid-lowering medication. Neither endothelium-independent **vasorelaxation**, assessed by sodium nitroprusside infusion, nor vasoconstriction induced by the nitric oxide blocker L-NMMA, were different between controls and patients, whether the latter were on or off lipid-lowering medication. Our results show an L-**arginine**-sensitive, impaired nitric-oxide-mediated vascular relaxation of forearm resistance vessels in hypercholesterolaemia which is reproducible, and reversible after short-term lipid-lowering therapy. Demonstration of such changes in this readily accessible vascular bed will allow larger trials assessing vascular function during lipid-lowering therapy to be done.

L11 ANSWER 13 OF 24 MEDLINE
AN 92031349 MEDLINE
DN 92031349
TI Hypercholesterolemia and atherosclerosis change vascular reactivity in rabbits by different mechanisms.
AU Galle J; Busse R; Bassenge E
CS Department of Applied Physiology, University of Freiburg, FRG.
SO ARTERIOSCLEROSIS AND THROMBOSIS, (1991 Nov-Dec) 11 (6) 1712-8. Journal code: AZ1. ISSN: 1049-8834.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199202
AB Vasomotor reactivity was assessed in vitro in arterial segments obtained from rabbits with different stages of atherosclerosis. Rabbits were fed a standard chow diet (controls) or a cholesterol-enriched diet to induce hypercholesterolemia and atherosclerosis. A third group received the hydroxymethylglutaryl coenzyme A reductase inhibitor, **lovastatin**, simultaneously with the cholesterol diet. Contractile responses of thoracic aortas to norepinephrine, serotonin, and potassium-rich solution, as well as endothelium-dependent dilations to acetylcholine, were compared after 2 and 4 months on the respective diet. Additionally, plasma cholesterol levels and the amount of plaques covering the intimal surface (as a percentage of the intimal surface) were determined; transmission electron microscopy of atherosclerotic arteries was also performed. After 2 months, the only difference was an enhancement of contractile responses to serotonin in the cholesterol-fed versus the control group. After 4 months on the

diet, contractile responses to serotonin were further enhanced, and norepinephrine- and potassium-induced vasoconstrictions were now also significantly enhanced in cholesterol-fed animals versus controls. Endothelium-dependent **vasodilations** were simultaneously reduced in cholesterol-fed animals. These alterations were partly prevented in cholesterol-fed and **lovastatin** -treated animals. Suppression of nitric oxide synthesis in control aortas by NG-nitro-L-**arginine** did not reveal any significant increases in contractile responses. Contractile responses to serotonin were enhanced after 2 months on the diet but before the appearance of intimal plaques, whereas attenuation of endothelium-dependent dilations, as well as the further enhancement of contractile responses to serotonin and to other agonists, were closely correlated with the degree of intimal plaques after 4 months on the diet.(ABSTRACT TRUNCATED AT 250 WORDS)

L11 ANSWER 14 OF 24 EMBASE COPYRIGHT 1998 ELSEVIER SCI. B.V.
AN 97247633 EMBASE
TI Dietary L-**arginine** reduces the progression of atherosclerosis in cholesterol-fed rabbits: Comparison with **lovastatin**.
AU Boger R.H.; Bode-Boger S.M.; Brandes R.P.; Phivthong-ngam L.; Bohme M.; Nafe R.; Mugge A.; Frolich J.C.
CS Dr. S.M. Bode-Boger, Institute of Clinical Pharmacology, Hannover Medical School, Konstanty-Gutschow-Str 8, 30625 Hannover, Germany, Federal Republic of
SO Circulation, (1997) 96/4 (1282-1290).
Refs: 42
ISSN: 0009-7322 CODEN: CIRCAZ
CY United States
DT Journal
FS 018 Cardiovascular Diseases and Cardiovascular Surgery
029 Clinical Biochemistry
037 Drug Literature Index
LA English
SL English
AB Background: We investigated whether L-**arginine** induces regression of preexisting atheromatous lesions and reversal of endothelial dysfunction in hypercholesterolemic rabbits, whether similar effects can be obtained by cholesterol-lowering therapy with **lovastatin**, and which mechanism leads to these effects.
Methods and Results: Rabbits were fed 1% cholesterol for 4 weeks and 0.5% cholesterol for an additional 12 weeks. Two groups of cholesterol-fed rabbits were treated with L-**arginine** (2.0% in drinking water) or **lovastatin** (10 mg/d) during weeks 5 through 16. Systemic nitric oxide (NO) formation was assessed as the urinary excretion rates of nitrate and cGMP in weekly intervals. Cholesterol feeding progressively reduced urinary nitrate excretion to .simeq.40% of baseline (P<.05) and increased plasma concentrations of asymmetrical dimethylarginine (ADMA), an endogenous NO synthesis inhibitor. Dietary L-**arginine** reversed the reduction in plasma L-**arginine**/ADMA ratio and partly restored urinary excretion of nitrate and cGMP (each P<.05 vs cholesterol) but did not change plasma cholesterol levels. L-**Arginine** completely blocked the progression of carotid intimal plaques, reduced aortic intimal thickening, and preserved endothelium-dependent **vasodilator** function.
Lovastatin treatment reduced plasma cholesterol by 32% but did not improve urinary nitrate or cGMP excretion or endothelium-dependent **vasodilation**. **Lovastatin** had a weaker inhibitory effect on carotid plaque formation and aortic intimal thickening than L-**arginine**. L-**Arginine** inhibited but **lovastatin** potentiated

superoxide radical generation in the atherosclerotic vascular wall. Conclusions: Dietary L-**arginine** improves NO-dependent **vasodilator** function in cholesterol-fed rabbits and completely blocks the progression of plaques via restoration of NO synthase substrate availability and reduction of vascular oxidative stress. **Lovastatin** treatment has a weaker inhibitory effect on the progression of atherosclerosis and no effect on vascular NO elaboration, which may be due to its stimulatory effect on vascular superoxide radical generation.

L11 ANSWER 15 OF 24 EMBASE COPYRIGHT 1998 ELSEVIER SCI. B.V.
AN 97084174 EMBASE
TI Endothelial dysfunction: Clinical implications.
AU Drexler H.
CS Germany, Federal Republic of
SO Progress in Cardiovascular Diseases, (1997) 39/4 (287-324).
Refs: 288
ISSN: 0033-0620 CODEN: PCVDAN
CY United States
DT Journal
FS 005 General Pathology and Pathological Anatomy
018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB The endothelium is involved in the control of vascular tone and homeostasis. Risk factors for arteriosclerosis, as well as other conditions have been shown to be associated with a dysfunctional endothelium. Clinically, endothelial function and dysfunction have been mostly evaluated by the assessment of endothelial dependent relaxation, for example in response to acetylcholine or increase inflow. The functional implications of endothelial dysfunction in cardiovascular disease are not well defined, but recent clinical trials have suggested that endothelial dysfunction may affect vascular tone and organ perfusion particularly during stress situations such as exercise. Moreover, endothelial dysfunction may represent an early event in the development of arteriosclerosis. Therefore, recent clinical studies have been performed to restore normal endothelial function in patients, using interventions such as L-**arginine**, lipid lowering drugs, vitamin C, other antioxidants, or exercise.

L11 ANSWER 16 OF 24 EMBASE COPYRIGHT 1998 ELSEVIER SCI. B.V.
AN 97069310 EMBASE
TI **Simvastatin**, an HMG-coenzyme A reductase inhibitor, improves endothelial function within 1 month.
AU O'Driscoll G.; Green D.; Taylor R.R.
CS Australia
SO Circulation, (1997) 95/5 (1126-1131).
Refs: 42
ISSN: 0009-7322 CODEN: CIRCAZ
CY United States
DT Journal
FS 006 Internal Medicine
018 Cardiovascular Diseases and Cardiovascular Surgery
037 Drug Literature Index
LA English
SL English
AB Background: Cholesterol-lowering therapy can improve cardiovascular morbidity and mortality in patients with atherosclerosis. Although the mechanisms responsible are unclear, these benefits precede macroscopic changes in the vasculature. Emerging evidence that

improvement in endothelial function may occur requires substantiation; in particular, it is unclear how early any such improvement would be detectable after initiation of therapy. Methods and Results: This randomized, double-blind, placebo- controlled crossover study evaluated the effect of **simvastatin** (20 mg daily for 4 weeks) on endothelium-dependent and endothelium-independent **vasodilation** and on the response to the inhibitor of nitric oxide synthesis, N(G)-monomethyl-L-**arginine** (L-NMMA), in the forearm vasculature of subjects with moderate elevation of total serum cholesterol (6.0 to 10.0 mmol/L) by use of strain-gauge plethysmography. Studies were repeated after 3 more months of open therapy. When the results are expressed as percentage changes in flow in the infused arm relative to the noninfused arm, the **vasodilator** response to acetylcholine was significantly increased after 4 weeks of treatment with **simvastatin** (P<.0005), and this improvement was further enhanced after 3 months (P<.005). Concurrently, **simvastatin** augmented the vasoconstrictor response to L-NMMA, an effect that was maintained at 3 months (P<.0005). The response to the endothelium-independent **vasodilator** sodium nitroprusside was unaltered. Conclusions: These observations indicate that within 1 month of treatment with **simvastatin**, both the stimulated and basal nitric oxide dilator functions of the endothelium are augmented, and the benefits of this HMG-coenzyme A reductase inhibitor persist with continued therapy.

L11 ANSWER 17 OF 24 EMBASE COPYRIGHT 1998 ELSEVIER SCI. B.V.
AN 96084390 EMBASE
TI Preservation of endothelium-dependent vascular relaxation in cholesterol-fed mice by the chronic administration of prazosin or **pravastatin**.
AU Kamata K.; Kojima S.; Sugiura M.; Kasuya Y.
CS Dept. Physiology and Morphology, Institute of Medicinal Chemistry, Hoshi University, Shinagawa-ku, Tokyo 142, Japan
SO Japanese Journal of Pharmacology, (1996) 70/2 (149-156).
ISSN: 0021-5198 CODEN: JJPAAZ
CY Japan
DT Journal
FS 018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB The relaxation of aortic rings in response to acetylcholine (ACh) was significantly decreased in cholesterol-fed mice. The attenuated relaxation in cholesterol-fed mice was preserved by the chronic administration of prazosin (20 mg/kg/day) or **pravastatin** (12.5 mg/kg/day). Serum low-density lipoprotein (LDL) levels were significantly increased in mice given cholesterol. The increased serum LDL levels in cholesterol-fed mice were returned to normal by the chronic administration of prazosin and **pravastatin**. A prior incubation of aortic rings with lysophosphatidylcholine (LPC) significantly attenuated ACh- and A23187-induced endothelium-dependent relaxation. The inhibitory effects of LPC on endothelium-dependent relaxation were not affected by indomethacin or superoxide dismutase. The sodium nitroprusside-induced relaxation of aortic rings was not changed by LPC. The inhibitory effects on ACh-induced relaxation by N(G)-monomethyl-L-**arginine** were restored by a prior exposure to L-**arginine**, whereas the inhibition of endothelium-dependent relaxation by LPC was not affected by L-**arginine**. These results suggest that cholesterol-fed mice are useful animal models of hypercholesterolemia, and chronic administration of prazosin or

pravastatin can preserve endothelium-dependent relaxation by lowering serum LDL in these animals. It is further suggested that LPC derived from oxidized LDL may be involved in the reduced endothelium-dependent relaxation in hyperlipidemia.

L11 ANSWER 18 OF 24 EMBASE COPYRIGHT 1998 ELSEVIER SCI. B.V.
AN 96013564 EMBASE
TI Lipid-lowering treatment: Effects on endothelial dysfunction.
AU Rubba P.; Mancini M.
CS Clinica Medica, Nuovo Policlinico, Federico II University, Via S. Pansini 5, 80131 Napoli, Italy
SO Current Opinion in Lipidology, (1995) 6/6 (348-353).
ISSN: 0957-9672 CODEN: COPLEU
CY United Kingdom
DT Journal
FS 005 General Pathology and Pathological Anatomy
018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB An association has been demonstrated between the extent of atherosclerotic involvement and **vasodilatory** capacity in coronary and cerebral circulation. Impairment of endothelium-dependent relaxation is inversely related to HDL concentrations in plasma. Angiographic studies in humans have shown improved **vasodilation** capacity of the coronary arteries after lipid-lowering treatment.

L11 ANSWER 19 OF 24 EMBASE COPYRIGHT 1998 ELSEVIER SCI. B.V.
AN 95255064 EMBASE
TI Vascular function in the forearm of hypercholesterolaemic patients off and on lipid-lowering medication.
AU Stroes E.S.G.; Koomans H.A.; De Bruin T.W.A.; Rabelink T.J.
CS Department Nephrology Hypertension, University Hospital, Heidelberglaan 100, 3584 CX Utrecht, Netherlands
SO Lancet, (1995) 346/8973 (467-471).
ISSN: 0140-6736 CODEN: LANCAO
CY United Kingdom
DT Journal
FS 006 Internal Medicine
018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB To study whether vascular dysfunction in hypercholesterolaemia is reversible, we investigated patients without overt arterial disease who were taking maintenance treatment for hypercholesterolaemia. Medication was stopped for 2 weeks, reinstituted for 12 weeks, and again stopped for 6 weeks. During both maintenance treatment and the 12 weeks of step-up medication the lipid profile was improved but did not return to normal. Dose-response curves for serotonin-induced **vasodilatation**, an index of nitric oxide-dependent **vasodilatation**, showed a comparable and significant rightward shift after a medication-free period of 2 and 6 weeks compared with control subjects, indicating endothelial dysfunction, which was already maximum after 2 weeks. After 12 weeks of lipid-lowering medication, the difference in endothelial function between controls and patients had disappeared. Co-infusion of L-**arginine**, the substrate for nitric oxide synthase, returned the impaired serotonin response during hypercholesterolaemia to normal, but had no effect on this response in controls or in

patients while on lipid-lowering medication. Neither endothelium-independent **vasorelaxation**, assessed by sodium nitroprusside infusion, nor vasoconstriction induced by the nitric oxide blocker L-NMMA, were different between controls and patients, whether the latter were on or off lipid-lowering medication. Our results show an L-**arginine**-sensitive, impaired nitric-oxide-mediated vascular relaxation of forearm resistance vessels in hypercholesterolaemia which is reproducible, and reversible after short-term lipid-lowering therapy. Demonstration of such changes in this readily accessible vascular bed will allow larger trials assessing vascular function during lipid-lowering therapy to be done.

L11 ANSWER 20 OF 24 EMBASE COPYRIGHT 1998 ELSEVIER SCI. B.V.
AN 92051423 EMBASE
TI Hypercholesterolemia and atherosclerosis change vascular reactivity in rabbits by different mechanisms.
AU Galle J.; Busse R.; Bassenge E.
CS Institut fur Angewandte Physiologie der Universitat, Hermann Herder Strasse 7, D-7800 Freiburg, Germany, Federal Republic of
SO ARTERIOSCLEROS. THROMB., (1991) 11/6 (1712-1718).
ISSN: 1049-8834 CODEN: ARTTE5
CY United States
DT Journal
FS 005 General Pathology and Pathological Anatomy
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB Vasomotor reactivity was assessed in vitro in arterial segments obtained from rabbits with different stages of atherosclerosis. Rabbits were fed a standard chow diet (controls) or a cholesterol-enriched diet to induce hypercholesterolemia and atherosclerosis. A third group received the hydroxymethylglutaryl coenzyme A reductase inhibitor, **lovastatin**, simultaneously with the cholesterol diet. Contractile responses of thoracic aortas to norepinephrine, serotonin, and potassium-rich solution, as well as endothelium-dependent dilations to acetylcholine, were compared after 2 and 4 months on the respective diet. Additionally, plasma cholesterol levels and the amount of plaques covering the intimal surface (as a percentage of the intimal surface) were determined; transmission electron microscopy of atherosclerotic arteries was also performed. After 2 months, the only difference was an enhancement of contractile responses to serotonin in the cholesterol-fed versus the control group. After 4 months on the diet, contractile responses to serotonin were further enhanced, and norepinephrine- and potassium-induced vasoconstrictions were now also significantly enhanced in cholesterol-fed animals versus controls. Endothelium-dependent **vasodilations** were simultaneously reduced in cholesterol-fed animals. These alterations were partly prevented in cholesterol-fed and **lovastatin**-treated animals. Suppression of nitric oxide synthesis in control aortas by N(G) nitro-L-**arginine** did not reveal any significant increases in contractile responses. Contractile responses to serotonin were enhanced after 2 months on the diet but before the appearance of intimal plaques, whereas attenuation of endothelium-dependent dilations, as well as the further enhancement of contractile responses to serotonin and to other agonists, were closely correlated with the degree of intimal plaques after 4 months on the diet. The similarity of alterations in vascular reactivity after 4 months on the diet to the effects of isolated low density lipoproteins on vascular tone and the correlation of these changes

with the degree of lipid-containing plaques support the hypothesis that lipoprotein accumulation in atherosclerotic arteries contributes to altered vascular reactivity.

L11 ANSWER 21 OF 24 USPATFULL
AN 97:112175 USPATFULL
TI Stable lipid emulsion
IN Suzuki, Hidekazu, Tokyo, Japan
Yamazaki, Satoshi, Tokyo, Japan
Naito, Yoshikazu, Tokyo, Japan
Endo, Kenji, Tokyo, Japan
Oguma, Touru, Tokyo, Japan
Maeda, Makoto, Tokyo, Japan
PA Wakamoto Pharmaceutical Co., Ltd., Tokyo, Japan (non-U.S. corporation)
PI US 5693337 971202
AI US 95-500087 950710 (8)
PRAI JP 94-183045 940713
DT Utility
EXNAM Primary Examiner: Kishore, Gollamudi S.
LREP Oblon, Spivak, McClelland, Maier & Neustadt, P.C.
CLMN Number of Claims: 8
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1775
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A lipid emulsion which comprises (A) an oil component, (B) an emulsifying agent containing yolk lecithin and/or soybean lecithin, and (C) water, wherein the lipid emulsion further comprises citric acid or a pharmaceutically acceptable salt thereof and at least one member selected from the group consisting of methionine, phenylalanine, serine, histidine and pharmaceutically acceptable salts thereof, provided that it does not simultaneously contain methionine and phenylalanine. The addition of citric acid and histidine, methionine, phenylalanine and/or serine to a lipid emulsion containing natural lecithin as an emulsifying agent permits the prevention of change of color and formation of oil drops associated with the conventional natural lecithin-containing lipid emulsion due to the synergistic effect of the foregoing additives. The drug-containing lipid emulsion is also excellent in storage stability and thus the foregoing lipid emulsion can be applied to drugs such as injections, eye drops, nasal drops, lotions or liniments, inhalants and drugs for oral administration or cosmetics such as humectants.

L11 ANSWER 22 OF 24 USPATFULL
AN 97:17918 USPATFULL
TI Compositions and methods for enhanced drug delivery
IN Hale, Ron L., Woodside, CA, United States
Lu, Amy, Los Altos, CA, United States
Solas, Dennis, San Francisco, CA, United States
Selick, Harold E., Belmont, CA, United States
Oldenburg, Kevin R., Fremont, CA, United States
Zaffaroni, Alejandro C., Atherton, CA, United States
PA Affymax Technologies N.V., Middlesex, England (non-U.S. corporation)
PI US 5607691 970304
AI US 95-449188 950524 (8)
RLI Continuation of Ser. No. US 93-164293, filed on 9 Dec 1993, now abandoned which is a continuation-in-part of Ser. No. US 93-77296, filed on 14 Jun 1993, now abandoned which is a continuation-in-part of Ser. No. US 92-898219, filed on 12 Jun 1992, now abandoned And a continuation-in-part of Ser. No. US

93-9463, filed on 27 Jan 1993, now abandoned
DT Utility
EXNAM Primary Examiner: Levy, Neil S.
LREP Stevens, Lauren L.
CLMN Number of Claims: 5
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 5349
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to methods of delivering pharmaceutical agents across membranes, including the skin layer or mucosal membranes of a patient. A pharmaceutical agent is covalently bonded to a chemical modifier, via a physiologically cleavable bond, such that the membrane transport and delivery of the agent is enhanced.

L11 ANSWER 23 OF 24 USPATFULL
AN 96:99020 USPATFULL
TI Stable aqueous dispersions containing liposomes
IN Endo, Kenji, Fujisawa, Japan
Suzuki, Hidekazu, Kanagawa-ken, Japan
Oguma, Touru, Hadano, Japan
Goto, Masayoshi, Tokyo, Japan
PA Wakamoto Pharmaceutical Co., Ltd., Tokyo, Japan (non-U.S. corporation)
PI US 5569464 961029
AI US 95-448972 950524 (8)
RLI Continuation of Ser. No. US 94-216854, filed on 24 Mar 1994, now abandoned
PRAI JP 93-98367 930402
DT Utility
EXNAM Primary Examiner: Kishore, Gollamudi S.
LREP Burns, Doane, Swecker & Mathis, LLP
CLMN Number of Claims: 7
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1405
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB An aqueous dispersion containing liposomes comprising yolk lecithin and/or soybean lecithin as lipids for forming liposomes wherein the dispersion contains a hydroxy acid and an amino acid, which hardly shows coloration, shows little leak of drugs encapsulated in the liposomes and is stable in a broad pH range.

L11 ANSWER 24 OF 24 USPATFULL
AN 95:58265 USPATFULL
TI Prodrugs for selective drug delivery
IN Mills, Randell L., R.D. #2, Cochranville, PA, United States 19330
PI US 5428163 950627
AI US 89-446439 891204 (7)
RLI Continuation-in-part of Ser. No. US 86-948326, filed on 31 Dec 1986, now abandoned
DT Utility
EXNAM Primary Examiner: Lee, Mary C.; Assistant Examiner: Powers, Fiona T.
LREP Lahive & Cockfield
CLMN Number of Claims: 1
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 2340
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A broad class of pharmaceutical agents which react directly with electron carriers or with reactive species produced by electron

transport to release a pharmacologically active molecule to effect a therapeutic functional change in the organism by a receptor or nonrecepter mediated action.

```
=> d his


     (FILE 'HOME' ENTERED AT 17:22:19 ON 28 JAN 1998)

     FILE 'BIOSIS, MEDLINE, EMBASE, USPATFULL, WPIDS' ENTERED AT
     17:25:03 ON 28 JAN 1998
L1          8321 S HMG-COA
L2          3111 S HMG-COA REDUCTASE INHIBITOR###
L3         12172 S (LOVASTATIN OR PRAVASTATIN OR SIMVASTATIN OR FLUVASTATI
L4         13086 S L2 OR L3
L5        139344 S ARGININE
L6           265 S L5 AND L4
L7        123146 S VASODILAT##### OR VASORELAX#######
L8            26 S L7 AND L6
L9           141 S L2 AND L5
L10            2 S L7 AND L9
L11           24 S L8 NOT L10

=> s l3 and l5

L12         255 L3 AND L5

=> s l7 and l12

L13          26 L7 AND L12

=> s l13 not l8

L14           0 L13 NOT L8
```

```
=> log y

COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY    SESSION
FULL ESTIMATED COST                              44.86      45.61

STN INTERNATIONAL LOGOFF AT 17:34:58 ON 28 JAN 1998
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FILE 'HOME' ENTERED AT 14:20:07 ON 28 JAN 1998

=> file ca

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.15	0.15

FILE 'CA' ENTERED AT 14:20:12 ON 28 JAN 1998
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1967 - 27 Jan 1998 (980127/ED) VOL 128 ISS 5

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> e lovastatin/cn

'CN' IS NOT A VALID EXPAND FIELD CODE FOR FILE 'CA'
The indicated field code is not available for EXPAND in this file. To see a list of expand field codes, at an arrow prompt (=>) enter "HELP EFIELDS FILE=" and the name the file from which you would like this information. For example, enter "HELP EFIELDS FILE=CA" to see in the list of expand field codes from the CA file.

=> file reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.32	0.47

FILE 'REGISTRY' ENTERED AT 14:20:31 ON 28 JAN 1998
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

STRUCTURE FILE UPDATES: 23 JAN 98 HIGHEST RN 200334-60-7
DICTIONARY FILE UPDATES: 27 JAN 98 HIGHEST RN 200334-60-7

TSCA INFORMATION NOW CURRENT THROUGH JUNE 1997

Please note that search-term pricing does apply when conducting SmartSELECT searches.

=> e lovastatin/cn

E1 1 LOVAGE OIL/CN

```
E2            1      LOVASICE S 2-1650/2/CN
E3            1 --> LOVASTATIN/CN
E4            1      LOVASTATIN 8'-(.ALPHA.-METHYLBUTYRYLOXY) ESTERASE/CN
E5            1      LOVASTATIN ACID/CN
E6            1      LOVASTATIN DIMER/CN
E7            1      LOVASTATIN DIOL LACTONE/CN
E8            1      LOVASTATIN ESTERASE/CN
E9            1      LOVASTATIN SODIUM SALT/CN
E10           1      LOVCHORRITE/CN
E11           1      LOVDARITE/CN
E12           1      LOVELLE/CN

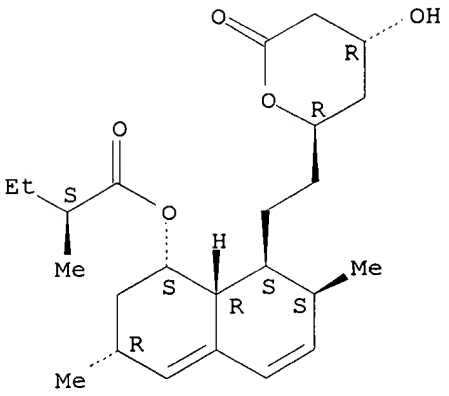
=> s e3

L1            1 LOVASTATIN/CN

=> d l1


L1   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 1998 ACS
RN   75330-75-5  REGISTRY
CN   Butanoic acid, 2-methyl-, 1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-
     (tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl
     ester, [1S-[1.alpha.(R*),3.alpha.,7.beta.,8.beta.(2S*,4S*),8a.beta.]
     ]- (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   (+)-Mevinolin
CN   Antibiotic MB 530B
CN   L 154803
CN   Lovastatin
CN   Mevacor
CN   Mevinolin
CN   MK 803
CN   Monacolin K
CN   Monacolin K lactone
CN   MSD 803
FS   STEREOSEARCH
DR   71949-96-7, 74133-25-8, 81739-26-6
MF   C24 H36 O5
CI   COM
LC   STN Files:   AGRICOLA, AIDSLINE, ANABSTR, BEILSTEIN*, BIOBUSINESS,
       BIOSIS, CA, CANCERLIT, CAPLUS, CASREACT, CEN, CHEMCATS,
       CHEMINFORMRX, CHEMLIST, CBNB, CIN, CJACS, CSCHEM, DDFU, DRUGNL,
       DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, HSDB*, IPA, MEDLINE, MRCK*,
       MSDS-OHS, NAPRALERT, PHAR, PNI, PROMT, RTECS*, SPECINFO, TOXLINE,
       TOXLIT, USPATFULL
         (*File contains numerically searchable property data)
     Other Sources:   WHO

Absolute stereochemistry.
```



841 REFERENCES IN FILE CA (1967 TO DATE)
39 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
842 REFERENCES IN FILE CAPLUS (1967 TO DATE)

```
=> e pravastatin/cn

E1            1      PRAVADOLINE MALEATE/CN
E2            1      PRAVAL/CN
E3            1 --> PRAVASTATIN/CN
E4            1      PRAVASTATIN DIOL LACTONE/CN
E5            1      PRAVASTATIN LACTONE/CN
E6            1      PRAVASTATIN SODIUM/CN
E7            1      PRAVOCAINE/CN
E8            1      PRAVOCAINE HYDROCHLORIDE/CN
E9            1      PRAVOTSEL W-O/CN
E10           1      PRAWOZELL WOFK/CN
E11           1      PRAXADINE/CN
E12           1      PRAXILENE/CN

=> se3

SE3 IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> s e3

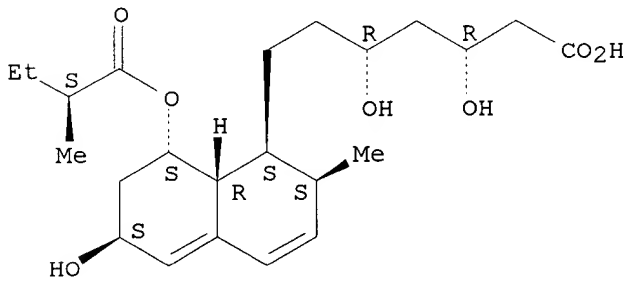
L2            1 PRAVASTATIN/CN

=> d l2


L2   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 1998 ACS
RN   81093-37-0  REGISTRY
CN   1-Naphthaleneheptanoic acid, 1,2,6,7,8,8a-hexahydro-.beta.,.delta.,6-
     trihydroxy-2-methyl-8-(2-methyl-1-oxobutoxy)-, [1S-
     [1.alpha.(.beta.S*,.delta.S*),2.alpha.,6.alpha.,8.beta.(R*),8a.alpha
     .]]- (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   Eptastatin
CN   Pravastatin
FS   STEREOSEARCH
DR   103382-89-4, 87068-19-7
MF   C23 H36 O7
CI   COM
LC   STN Files:   AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, CA,
```

CANCERLIT, CAPLUS, CASREACT, CEN, CBNB, CIN, CJACS, DDFU, DRUGNL,
DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, MEDLINE, NAPRALERT,
PHAR, PNI, PROMT, TOXLINE, TOXLIT, USPATFULL
(*File contains numerically searchable property data)
Other Sources: WHO

Absolute stereochemistry.



434 REFERENCES IN FILE CA (1967 TO DATE)
6 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
436 REFERENCES IN FILE CAPLUS (1967 TO DATE)

=> e simvastatin/cn

E1	1	SIMUSOL/CN
E2	1	SIMUVAX/CN
E3	1 -->	SIMVASTATIN/CN
E4	1	SIMVASTATIN ACID/CN
E5	1	SIN 1/CN
E6	1	SIN 1.2056/CN
E7	2	SIN 10/CN
E8	1	SIN 10 (PHARMACEUTICAL)/CN
E9	1	SIN 1A/CN
E10	1	SIN 1C/CN
E11	1	SIN 3/CN
E12	1	SIN 620/CN

=> s e3

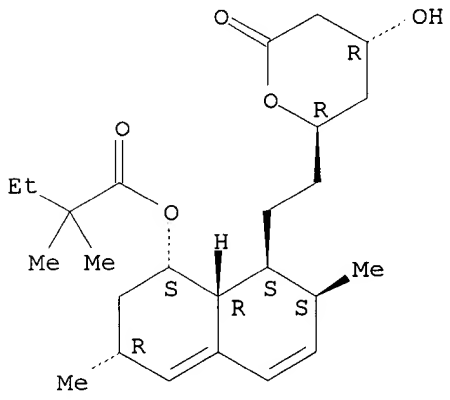
L3 1 SIMVASTATIN/CN

=> d l3

L3 ANSWER 1 OF 1 REGISTRY COPYRIGHT 1998 ACS
RN 79902-63-9 REGISTRY
CN Butanoic acid, 2,2-dimethyl-, 1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1.alpha.,3.alpha.,7.beta.,8.beta.(2S*,4S*),8a.beta.]]-(9CI) (CA INDEX NAME)
OTHER NAMES:
CN L 644128-000U
CN MK 733
CN **Simvastatin**
CN Synvinolin
CN Velostatin
CN Zocor
FS STEREOSEARCH
DR 98609-43-9, 118607-03-7

MF C25 H38 O5
CI COM
LC STN Files: AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, CA, CANCERLIT, CAPLUS, CASREACT, CEN, CHEMCATS, CHEMLIST, CBNB, CIN, CJACS, DDFU, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, MEDLINE, MRCK*, NAPRALERT, PHAR, PNI, PROMT, RTECS*, TOXLINE, TOXLIT, USPATFULL
(*File contains numerically searchable property data)
Other Sources: WHO

Absolute stereochemistry.



451 REFERENCES IN FILE CA (1967 TO DATE)
6 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
452 REFERENCES IN FILE CAPLUS (1967 TO DATE)

=> e fluvastatin/cn

E1	1	FLUVALINATE-MALATHION MIXT./CN
E2	1	FLUVAROL/CN
E3	1 -->	FLUVASTATIN/CN
E4	1	FLUVASTATIN SODIUM/CN
E5	1	FLUVET/CN
E6	1	FLUVIBACTIN/CN
E7	1	FLUVIBACTINE/CN
E8	1	FLUVIOL A/CN
E9	1	FLUVIOL B/CN
E10	1	FLUVIOL C/CN
E11	1	FLUVIOL D/CN
E12	1	FLUVIOL E/CN

=> s e3

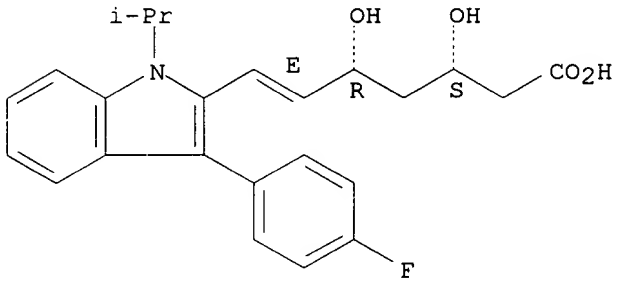
L4 1 FLUVASTATIN/CN

=> d l4

L4 ANSWER 1 OF 1 REGISTRY COPYRIGHT 1998 ACS
RN 93957-54-1 REGISTRY
CN 6-Heptenoic acid, 7-[3-(4-fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl]-3,5-dihydroxy-, [R*,S*-(E)]- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 6-Heptenoic acid, 7-[3-(4-fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl]-3,5-dihydroxy-, [R*,S*-(E)]-(.+-.)-

OTHER NAMES:
CN **Fluvastatin**
FS STEREOSEARCH
MF C24 H26 F N O4
CI COM
LC STN Files: AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, CA, CAPLUS, CBNB, CIN, CJACS, DDFU, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, MRCK*, PNI, PROMT, TOXLINE, TOXLIT, USPATFULL
(*File contains numerically searchable property data)
Other Sources: WHO

Relative stereochemistry.
Double bond geometry as shown.



147 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
147 REFERENCES IN FILE CAPLUS (1967 TO DATE)

=> e dalvastatin/cn

E1 1 DALTROBAN/CN
E2 1 DALUR/CN
E3 1 --> DALVASTATIN/CN
E4 1 DALVIN 1067/CN
E5 1 DALVIN 1467/CN
E6 1 DALVOR/CN
E7 1 DALVOR 720/CN
E8 1 DALYDE/CN
E9 1 DALYITE/CN
E10 1 DALYITE (K2ZR(SI2O5)3)/CN
E11 1 DALYITE, TITANIAN (K2SI6(ZR0.5-0.9TI0.1-0.5)O15)/CN
E12 1 DALZIC/CN

=> s e3

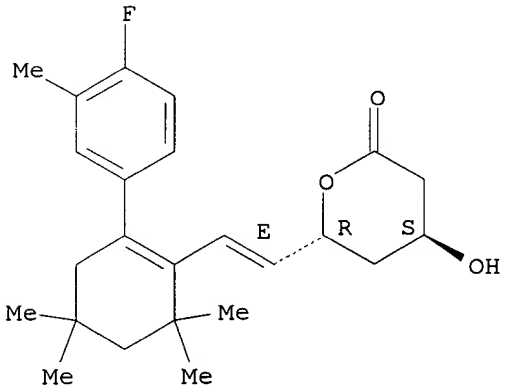
L5 1 DALVASTATIN/CN

=> d l5

L5 ANSWER 1 OF 1 REGISTRY COPYRIGHT 1998 ACS
RN 132100-55-1 REGISTRY
CN 2H-Pyran-2-one, 6-[2-[2-(4-fluoro-3-methylphenyl)-4,4,6,6-tetramethyl-1-cyclohexen-1-yl]ethenyl]tetrahydro-4-hydroxy-, [4.alpha.,6.beta.(E)]- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 2H-Pyran-2-one, 6-[2-[2-(4-fluoro-3-methylphenyl)-4,4,6,6-tetramethyl-1-cyclohexen-1-yl]ethenyl]tetrahydro-4-hydroxy-, [4.alpha.,6.beta.(E)]-(.+-.)-
OTHER NAMES:
CN **Dalvastatin**

CN RG 12561
FS STEREOSEARCH
MF C24 H31 F O3
CI COM
SR World Health Organization
LC STN Files: BIOBUSINESS, BIOSIS, CA, CAPLUS, DRUGNL, DRUGPAT, DRUGUPDATES, EMBASE, IPA, PHAR, PNI, PROMT, TOXLINE, TOXLIT, USPATFULL

Relative stereochemistry.
Double bond geometry as shown.



7 REFERENCES IN FILE CA (1967 TO DATE)
7 REFERENCES IN FILE CAPLUS (1967 TO DATE)

=> e compactin/cn

E1	1	COMPACT ENAMEL BOND/CN
E2	1	COMPACTAL ACU/CN
E3	2 -->	COMPACTIN/CN
E4	1	COMPACTIN (GENISTA)/CN
E5	1	COMPACTIN (PENICILLIUM)/CN
E6	1	COMPACTIN ACID/CN
E7	1	COMPACTIN DIOL LACTONE/CN
E8	1	COMPACTIN SODIUM SALT/CN
E9	1	COMPACTINERVINE/CN
E10	1	COMPACTINERVINE 19-ACETATE/CN
E11	1	COMPACTINERVINE HYDROBROMIDE/CN
E12	1	COMPACTINERVINE HYDROCHLORIDE/CN

=> s e3

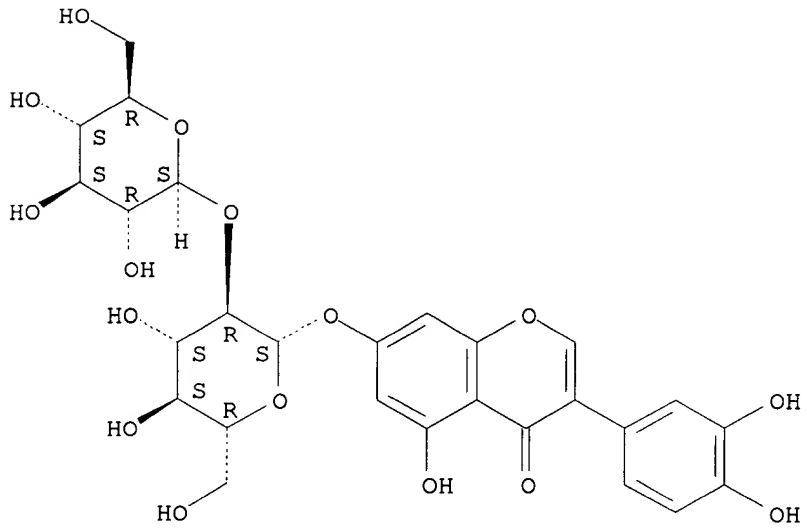
L6 2 COMPACTIN/CN

=> d l6

L6 ANSWER 1 OF 2 REGISTRY COPYRIGHT 1998 ACS
RN 101072-83-7 REGISTRY
CN 4H-1-Benzopyran-4-one, 3-(3,4-dihydroxyphenyl)-7-[(2-O-.beta.-D-glucopyranosyl-.beta.-D-glucopyranosyl)oxy]-5-hydroxy- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **Compactin**
CN Compactin (Genista)

FS STEREOSEARCH
MF C27 H30 O16
SR CA
LC STN Files: AGRICOLA, BEILSTEIN*, BIOBUSINESS, BIOSIS, CA, CAPLUS, CEN, CIN, PNI, PROMT, TOXLIT, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry.



3 REFERENCES IN FILE CA (1967 TO DATE)
3 REFERENCES IN FILE CAPLUS (1967 TO DATE)

=> file ca

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	30.00	30.47

FILE 'CA' ENTERED AT 14:23:54 ON 28 JAN 1998
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1967 - 27 Jan 1998 (980127/ED) VOL 128 ISS 5

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d his

(FILE 'HOME' ENTERED AT 14:20:07 ON 28 JAN 1998)

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FILE 'REGISTRY' ENTERED AT 14:20:31 ON 28 JAN 1998

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                E LOVASTATIN/CN
L1            1 S E3
                E PRAVASTATIN/CN
L2            1 S E3
                E SIMVASTATIN/CN
L3            1 S E3
                E FLUVASTATIN/CN
L4            1 S E3
                E DALVASTATIN/CN
L5            1 S E3
                E COMPACTIN/CN
L6            2 S E3
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FILE 'CA' ENTERED AT 14:23:54 ON 28 JAN 1998

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=> s l1

L7          859 L1

=> d l7 200-205 bib,ab
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L7 ANSWER 200 OF 859 CA COPYRIGHT 1998 ACS
AN 124:164586 CA
TI Lipid metabolism as a target for brain cancer therapy: synergistic activity of lovastatin and sodium phenylacetate against human glioma cells
AU Prasanna, Premakala; Thibault, Alain; Liu, Lei; Samid, Dvorit
CS Clinical Pharmacology Branch, National Cancer Inst., Bethesda, MD, USA
SO J. Neurochem. (1996), 66(2), 710-16
CODEN: JONRA9; ISSN: 0022-3042
DT Journal
LA English
AB Malignant gliomas, the most common form of primary brain tumors, are highly dependent on the mevalonate (MVA) pathway for the synthesis of lipid moieties crit. to cell replication. Human glioblastoma cells were uniquely vulnerable to growth arrest by lovastatin, a competitive inhibitor of the enzyme regulating MVA synthesis, 3-hydroxy-3-methylglutaryl CoA reductase. The sodium salt of phenylacetic acid (NaPA), an inhibitor of MVA-pyrophosphate decarboxylase, the enzyme that controls MVA use, acted synergistically with lovastatin to suppress malignant growth. When used at pharmacol. attainable concns., the two compds. induced profound cytostasis and loss of malignant properties such as invasiveness and expression of the transforming growth factor-.beta.2 gene, coding for a potent immunosuppressive cytokine. Supplementation with exogenous ubiquinone, an end product of the MVA pathway, failed to rescue the cells, suggesting that decreased synthesis of intermediary products are responsible for the antitumor effects obsd. In addn. to blocking the MVA pathway, lovastatin alone and in combination with NaPA increased the expression of the peroxisome proliferator-activated receptor, a transcription factor implicated in the control of lipid metab., cell growth, and differentiation. The results indicate that targeting lipid metab. with lovastatin, used alone or in combination with the arom. fatty acid NaPA, may offer a novel approach to the treatment of malignant gliomas.

L7 ANSWER 201 OF 859 CA COPYRIGHT 1998 ACS
AN 124:135360 CA
TI Effects of cholesterol lowering on the progression of coronary

atherosclerosis in women. A Canadian Coronary Atherosclerosis Intervention Trial (CCAIT) substudy
AU Waters, David; Higginson, Lyall; Gladstone, Peter; Boccuzzi, Stephen J.; Cook, Thomas; Lesperance, Jacques
CS Division Cardiology, Hartford Hospital, Hartford, CT, 06102-5037, USA
SO Circulation (1995), 92(9), 2404-10
CODEN: CIRCAZ; ISSN: 0009-7322
DT Journal
LA English
AB Although coronary disease is the leading cause of death in women and its clin. features differ from those in men, very few women have been included in angiog. trials of cholesterol lowering. Sixty-two women with diffuse but not necessarily severe coronary atherosclerosis documented on a recent angiogram and with fasting serum cholesterol between 220 and 300 mg/dL were enrolled in a double-blind, placebo-controlled trial. More than one half had a history of hypertension, approx. one quarter were diabetics, and one third were current smokers. All women received dietary counseling. Lovastatin or placebo was begun at 20 mg/d and was titrated if necessary to 40 and then to 80 mg during the first 16 wk to attain a fasting LDL cholesterol .ltoreq.130 mg/dL. The mean lovastatin dose was 34 mg/d. Total and LDL cholesterol decreased by 24% and 32%, resp., in lovastatin-treated women but by <3% in women receiving placebo. Coronary arteriog. was repeated after 2 yr in 54 women (87%), and their 394 lesions were measured "blindly" on pairs of film with an automated computerized quant. system. Progression, defined as a worsening in min. diam. of one or more stenoses by .gtoreq.0.4 mm, occurred in 7 of 25 lovastatin-treated women and 17 of 29 placebo-treated women (28% vs. 59%, P=.031). New coronary lesions developed in 1 lovastatin-treated woman and 13 placebo-treated women (4% vs. 45%, P<.001). The outcome for each of the angiog. end points was not significantly different between the women and the 245 men who completed the trial. Lovastatin slows the progression of coronary atherosclerosis and prevents the development of new coronary lesions in women.

L7 ANSWER 202 OF 859 CA COPYRIGHT 1998 ACS
AN 124:127144 CA
TI Oral pharmaceutical controlled-release liquid suspension containing oils and polymers and antioxidants
IN Modi, Pankaj
PA Can.
SO Can. Pat. Appl., 18 pp.
CODEN: CPXXEB
PI CA 2143070 AA 950823
AI CA 95-2143070 950221
PRAI US 94-199933 940222
DT Patent
LA English
AB A controlled-release oral formulation for use with a variety of drugs, e.g. anti-Parkinsonian, cardiovascular and anti-epileptic drugs are formed in liq. suspension form. The ingredients in the suspension are water, and edible oil and a stabilizer for the liq. suspension, at least one pharmaceutically active ingredient, at least two water sol. biodegradable polymers, and optionally with at least one antioxidant to prevent degrdn. and oxidn. of the pharmaceutically active ingredients. A typical tsp dose of anti-Parkinson liq. suspension contains 15-150 mg carbidopa, 50-1500 mg levodopa, 100-300 mg of a combination of polyvinyl alc. and polysucrose, 10-50 mg oil, 5-15 mg antioxidant, e.g. vitamin E, 5-20 mg stabilizer, 10-15 mg colorants, 10-15 mg natural flavoring agents and 5 mL water.

L7 ANSWER 203 OF 859 CA COPYRIGHT 1998 ACS
AN 124:116926 CA
TI 3,4-Dehydro-2-hydroxy-6-(2-phenethyl)tetrahydropyran. 1,3-Acyclic diastereoselection in reaction with MeOH and its application in the synthesis of a racemic mevinolin analog
AU Yadav, Veejendra K.; Kapoor, Kamal K.
CS Dep. Chem., Indian Inst. Technol., Kanpur, 208 016, India
SO Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem. (1996), 35B(1), 8-13
CODEN: IJSBDB; ISSN: 0376-4699
DT Journal
LA English
OS CASREACT 124:116926
AB 3,4-Dehydro-2-hydroxy-6-(2-phenethyl)tetrahydropyran and its dimer both react with MeOH in the presence of a catalytic amt. of concd. HCl to provide 2,4-dimethoxy-6-(2-phenylethyl)tetrahydropyran with a decent level of 1,3-acyclic diastereoselection in favor of the 4,6-trans deriv. The ratio of the arabino and xylo structures was an unprecedented 4:1. Models to account for the obsd. diastereoselectivity are discussed. Further transformation to the 2-oxo deriv. and unmasking of the 4-OH function provide a rapid entry into the racemic mevinolin analog I.

L7 ANSWER 204 OF 859 CA COPYRIGHT 1998 ACS
AN 124:106561 CA
TI Lipid clearing agents in steroid-induced osteoporosis
AU Wang, Gwo-Jaw; Chung, Kao-Chi; Shen, Wun-Jer
CS School Medicine, University Virginia, Charlottesville, VA, 22908, USA
SO J. Formosan Med. Assoc. (1995), 94(10), 589-92
CODEN: JFASEO; ISSN: 0929-6646
DT Journal
LA English
AB Osteoporosis is a major complication of long-term steroid use. In this exptl. study, the effect of lipid clearing agents on the preservation of bone mass was assessed. New Zealand white rabbits were divided into four groups: normal control, steroid-only, steroid plus lovastatin, and steroid plus bezafibrate. Treatments were continued for either 6 to 8 wk or 13 to 15 wk, after which the rabbits were sacrificed. Each rabbit's trabecular bone area from the central sagittal sections of the femoral head was measured. At 6 to 8 wk there was no significant difference between the steroid groups, but at 13 to 15 wk the bone area in the steroid-only group was significantly lower than in the groups that had also received lipid clearing agents. Histol. examn. of livers from the normal control group showed significantly less degeneration than in all of the steroid groups. Lipid clearing agents appear to maintain bone mass in the femoral head, but do not avert fatty changes in the liver in steroid treated rabbits. Concomitant use of lipid clearing agents with steroids may have the potential to decrease the severity of steroid induced osteoporosis.

L7 ANSWER 205 OF 859 CA COPYRIGHT 1998 ACS
AN 124:106186 CA
TI Effect of in vivo and in vitro lovastatin treatment on mast cell activation
AU Roche, C. M.; Trimble, E. R.; Ennis, M.
CS Institute Clinical Science, Queen's University Belfast, Belfast, BT12 6BJ, UK
SO Int. Arch. Allergy Immunol. (1995), 108(3), 240-6
CODEN: IAAIEG; ISSN: 1018-2438
DT Journal

LA English
AB The hydroxymethylglutaryl (HMG) CoA reductase inhibitor lovastatin is used to treat hyperlipidemia. This agent prevents the isoprenylation of some proteins involved in signal transduction processes and inhibits IgE-receptor-linked mediator release from RBL-2H3 cells. In this study the effect of in vivo and in vitro administration of lovastatin on histamine release from rat peritoneal mast cells was examd. Lovastatin (4 mg/kg/day for 2 wk) inhibited histamine release induced by Con A from rat peritoneal mast cells of Hooded-Lister rats and both homozygous lean and obese Zucker rats. In contrast, release induced by antirat IgE (anti-IgE) was only significantly inhibited in cells derived from Hooded-Lister rats and that induced by compd. 48/80 was not altered. Lovastatin (20 .mu.M, 24 h, in vitro) caused a significant inhibition of the subsequent histamine release to Con A, anti-IgE and compd. 48/80 but not to the calcium ionophore A 23187. It is important to det. whether such inhibitory effects are also obsd. after the chronic, clin. administration of lovastatin and other HMG CoA reductase inhibitors.

=> s l2

L8 434 L2

=> d l8 200-205 bib,ab

L8 ANSWER 200 OF 434 CA COPYRIGHT 1998 ACS
AN 123:306243 CA
TI Cholesterol and recurrent events: a secondary prevention trial for normolipidemic patients
AU Pfeffer, Marc A.; Sacks, Frank M.; Moye, Lemuel A.; Brown, Lisa; Rouleau, Jean L.; Hartley, L. Howard; Rouleau, Jacques; Grimm, Richard; Sestier, Francois; et al.
CS Harvard Medical School, Bringham and Women's Hosp., Boston, MA, 02115, USA
SO Am. J. Cardiol. (1995), 76(9), 98c-106c
CODEN: AJCDAG; ISSN: 0002-9149
DT Journal
LA English
AB Although elevated plasma cholesterol levels represent a well-established and significant risk for developing atherosclerosis, there is a wide spectrum of cholesterol levels in patients with coronary artery disease (CAD). Most secondary prevention studies have generated convincing evidence that cholesterol redn. in patients with high cholesterol levels is assocd. with improved clin. outcome by reducing risk of further cardiovascular events. However, other risk factors may play a prominent role in the pathogenesis of coronary disease in the majority of patients with near-normal cholesterol values. The Cholesterol and Recurrent Events (CARE) study was designed to address whether the pharmacol. redn. of cholesterol levels with the 3-hydroxy-3-methyglutaryl CoA (HMG-CoA) reductase inhibitor, pravastatin, would reduce the sum of fatal coronary artery disease (CAD) and nonfatal myocardial infarction (MI) in patients who have survived an MI yet have a total cholesterol value <240 mg/dL (<6.2 mmol/L). The other inclusion criteria for this study were age 21-75 yr, low d. lipoprotein (LDL) cholesterol levels of 115-174 mg/dL (3.0-4.5 mmol/L), and fasting serum triglyceride levels <350 mg/dL (<4.0 mmol/L). A total of 4,159 eligible consenting patients without other study exclusions were then randomly assigned to receive either pravastatin 40 mg daily or matching placebo in addn. to their individualized conventional therapy. The trial was

designed to have a median follow-up of 5 yr. Study endpoints will be evaluated with respect to predefined subgroups according to baseline lipid values, age, gender, prior cardiovascular risk factors, and history. The CARE study should add important and unique information to the evolving field of cholesterol redn. in patients with ischemic heart disease by directly testing the question of whether pharmacol. cholesterol redn. benefits the majority of patients with CAD and cholesterol levels <240 mg/dL (<6.2 mmol/L).

L8 ANSWER 201 OF 434 CA COPYRIGHT 1998 ACS
AN 123:306241 CA
TI Reduction in coronary events during treatment with pravastatin
AU Furberg, Curt D.; Pitt, Bertram; Byington, Robert P.; Park, Jong-Soon; McGovern, Mark E.
CS Medical Center Blvd., Bowman Gray School of Medicine, Winston-Salem, NC, USA
SO Am. J. Cardiol. (1995), 76(9), 60c-3c
CODEN: AJCDAG; ISSN: 0002-9149
DT Journal
LA English
AB The 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) reductase inhibitors, or stains, are more efficacious than older lipid-lowering agents and therefore may be more effective in reducing the incidence of coronary events. The objective of this prespecified anal. was to examine in coronary patients the effect of the lipid-lowering agent pravastatin on 3-yr rates of coronary event incidence, all-cause mortality, and nonfatal myocardial infraction (MI), and to det. whether any obsd. benefit was also evident in patients >65 yr of age. The design of this anal. was to pool the data from 2 concurrent 3-yr placebo-controlled clin. trails of pravastatin monotherapy in coronary patients (Pravastatin Limitation of Atherosclerosis in the Coronary Arteries [PLAC I] and the Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries [PLAC II]). This pooled database included 559 coronary patients with moderately elevated levels of low d. lipoprotein cholesterol (between the 60th and 90th percentiles for age and gender in the United States). Over the 3 yr of follow-up, use of pravastatin was assocd. with a 55% redn. in coronary incidence (p=0.014). Pravastatin was also assocd. with a 67% redn. in nonfatal MI (p=0.006). Eleven placebo patients died over the 3 yr of follow-up compared with 7 in the pravastatin groups (a 40% redn.). Among older patients (age.gtoreq.65 yr), pravastatin therapy was assocd. with a 79% redn. in coronary event incidence (95% confidence interval [CI] 33-100%) and with a 86% redn. in nonfatal myocardial infarction (CI, 35-100%). These results provide strong evidence that pravastatin prevents recurrent clin. events in coronary patients, including those .gtoreq.65 yr of age.

L8 ANSWER 202 OF 434 CA COPYRIGHT 1998 ACS
AN 123:306240 CA
TI Pravastatin, lipids, and atherosclerosis in the carotid arteries (PLAC-II)
AU Byington, Robert Patrick; Furberg, Curt Daniel; Crouse, John Robert, III; Espeland, Mark Andrew; Bond, M. Gene
CS Medical Center Blvd., Bowman Gray School of Medicine, Winston Salem, NC, USA
SO Am. J. Cardiol. (1995), 76(9), 54c-9c
CODEN: AJCDAG; ISSN: 0002-9149
DT Journal
LA English
AB The Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries trial (PLAC-II) was initiated in 1987 and was the first

double-blind, randomized clin. trial with progression of early extracranial carotid atherosclerosis as an outcome variable. We randomized 151 coronary patients to placebo or pravastatin and treated them for 3 yr. B-mode ultrasound quantification of carotid artery intimal-medial thickness (IMT) was obtained at baseline and sequentially during this period. The primary outcome was the change in the mean of the max. IMT measurements over time. Effects on individual carotid artery segments (common, bifurcation, internal carotid artery) and on clin. events were also investigated. During follow-up, plasma concns. of total cholesterol were lower in pravastatin-treated patients compared with those of placebo-treated patients (4.81 vs 6.08 mmol/L [186 vs 235 mg/dL]) as were concns. of low d. lipoprotein (LDL) cholesterol (3.10 vs 4.29 mmol/L [120 vs 167 mg/dL]). Plasma concns. of high d. lipoprotein2 (HDL2) cholesterol were higher in pravastatin-treated patients than in placebo-treated patients (0.16 vs 0.14 mmol/L [6.1 vs 5.5 mg/dL]). Active treatment resulted in a nonsignificant 12% redn. in progression of the mean-max. IMT (from 0.068 mm/yr placebo to 0.059 mm/yr pravastatin) and a statistically significant 35% redn. in IMT progression in the common carotid (p=0.03). Active treatment was also assocd. with a 60% redn. of nonfatal myocardial infarction plus death caused by coronary artery disease (p=0.04), and an 80% redn. of fatal plus any nonfatal myocardial infarction (p=0.03).

L8 ANSWER 203 OF 434 CA COPYRIGHT 1998 ACS
AN 123:305806 CA
TI Prospective meta-analysis of cholesterol-lowering studies: the Prospective Pravastatin Pooling (PPP) Project and the Cholesterol Treatment Trialists (CTT) collaboration
AU Simes, R. John
CS Clinical Trials Centre, Univ. of Sydney, Sydney, 2006, Australia
SO Am. J. Cardiol. (1995), 76(9), 122c-6c
CODEN: AJCDAG; ISSN: 0002-9149
DT Journal; General Review
LA English
AB Review with 32 refs. Meta-analyses of randomized trials evaluating cholesterol-lowering therapy have demonstrated clear redns. in coronary events and coronary mortality. However, the treatment impact on total mortality has been less certain. With the variable selection of trials and treatment questions, results of meta-analyses have sometimes given conflicting conclusions regarding the magnitude of treatment effects and the populations to whom benefits might accrue. Prospective meta-anal. can avoid these problems by clearly specifying the research questions, eligible studies, anal. plans, and outcome definitions in advance of trial results publication. This approach has been adopted in 2 major prospective meta-analyses of cholesterol-lowering treatments: the Prospective Pravastatin Pooling (PPP) project and the Cholesterol Treatment Trialists (CTT) collaboration. The PPP project is a prospectively planned combined anal. of 3 large-scale pravastatin trials comparing pravastatin against placebo over a min. 5-yr period. The anal. will contain data for >19,500 patients and should have the power to examine the effects of treatment on total mortality, coronary mortality, and incidence of cancers as well as the ability to look at total coronary events in important subgroups underrepresented in previous trials. The CTT collaboration is a planned prospective meta-anal. of 12 major ongoing or planned randomized trails evaluating therapy with 3-hydroxy-3-methylglutaryl CoA reductase inhibitors, a fibrate, or dietary modification. The trials were prospectively registered and the CTT protocols became final in Nov. 1994. By the year 2000, the CTT collaboration is projected to have information on about 65,000 patients. This enormous data set will provide more reliable ests. of the effects of

cholesterol redn. on cause-specific mortality and of effects on coronary mortality within important subgroups.

L8 ANSWER 204 OF 434 CA COPYRIGHT 1998 ACS
AN 123:282735 CA
TI Pravastatin modulates cholesteryl ester transfer from HDL to ApoB-containing lipoproteins and lipoprotein subspecies profile in familial hypercholesterolemia
AU Guerin, Maryse; Dolphin, Peter J.; Talussot, Corinne; Gardette, Jean; Berthezene, Francois; Chapman, M. John
CS Pavillion Benjamin Delessert, Hopital de la Pitie, Paris, 75651, Fr.
SO Arterioscler., Thromb., Vasc. Biol. (1995), 15(9), 1359-68
CODEN: ATVBFA; ISSN: 1079-5642
DT Journal
LA English
AB Familial hypercholesterolemia (FH) results from genetic defects in the LDL receptor, and is characterized by a marked elevation in plasma LDL and by qual. abnormalities in LDL particles. Because LDL particles are major acceptors of cholesteryl esters (CEs) from HDL, significant changes occur in the flux of CE through the reverse cholesterol pathway. To evaluate the effects of an HMG-CoA reductase inhibitor, pravastatin, on CE transfer from HDL to apo-B-contg. lipoproteins and on plasma lipoprotein subspecies profile in subjects with heterozygous FH, we investigated the transfer of HDL-CE to LDL subfractions and changes in both concn. and chem. compn. of the apo B- and the apo AI-contg. lipoproteins. After pravastatin treatment (40 mg/d) for a 12-wk period, plasma LDL concns. (mean .+-. SD, 745.4 .+-. 51.9 mg/dL) were reduced by 36% in patients with FH (n = 6). By contrast, the qual. features of the d. profile of LDL subspecies in patients with FH, in whom the intermediate (d = 1.029 to 1.039 g/mL) and dense (d = 1.039 to 1.063 g/mL) subspecies were significantly increased relative to a control group, were not modified by pravastatin. In addn., no significant effect on the chem. compn. of individual LDL subfractions was obsd. Furthermore, plasma HDL concns. were not modified, although the d. distribution of HDL was normalized. Indeed, the HDL d. peak was shifted towards the HDL2 subfraction (ratios of HDL2 to HDL3 were 0.7 and 1.1 before and after treatment, resp.). Evaluation of plasma CE transfer protein (CETP) mass was performed with an exogenous CE transfer assay. Under these conditions, no modification of plasma CETP protein mass was induced by pravastatin administration. However, the rate of CE transfer from HDL to LDL was reduced by 24% by pravastatin (61 .+-. 17 .mu.g CE.h-1.mL-1 plasma; P <.0005), although intermediate and dense LDL subfractions again accounted for the majority (71%) of the total CE transferred to LDL. Thus, pravastatin induced redn. of plasma CETP activity without change in the preferential targeting of the transfer of HDL-CE towards the denser LDL subfractions. In conclusion, pravastatin reduces the elevated flux of CE from HDL to apo B-contg. lipoproteins in subjects with heterozygous FH as a result of a redn. in the LDL particle acceptor concn.

L8 ANSWER 205 OF 434 CA COPYRIGHT 1998 ACS
AN 123:276044 CA
TI Hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitor for preventing or reducing risks of onset of cardiovascular events
IN Behounek, Bruce D.; McGovern, Mark E.; Olukotun, Adeoye Y.
PA Bristol-Myers Squibb Co., USA
SO Eur. Pat. Appl., 19 pp.
CODEN: EPXXDW
PI EP 671171 A1 950913
DS R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE

AI EP 95-100353 950112
PRAI US 94-182471 940118
DT Patent
LA English
AB A method is provided for preventing or reducing the risk of onset of a cardiovascular event by administering an HMG-CoA reductase inhibitor such as pravastatin to a patient who has .gtoreq.1 risk factor for a coronary and/or cerebrovascular event such as hypercholesterolemia. This, patients given 20 mg pravastatin/day for 13 wk showed redns. in plasma LDL cholesterol, total cholesterol, and triglycerides of 26, 19, and 12%, resp. Tablets were prepd. contg. pravastatin 7, lactose 67, microcryst. cellulose 20, croscarmellose Na 2, Mg stearate 1, and MgO 3 parts.

=> s l3

L9 454 L3

=> d l9 200-205 bib,ab

L9 ANSWER 200 OF 454 CA COPYRIGHT 1998 ACS
AN 122:282211 CA
TI Method of detecting cytopenia that is mediated by drug-dependent antibody binding to blood cells
IN Aster, Richard H.; Curtis, Brian R.
PA Blood Center of Southeastern Wisconsin, Inc., USA
SO PCT Int. Appl., 42 pp.
CODEN: PIXXD2
PI WO 9508116 A1 950323
DS W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG
AI WO 94-US10333 940915
PRAI US 93-120837 930915
DT Patent
LA English
AB Drug-dependent antibodies that bind to granulocytes, erythrocytes, platelets or membrane proteins derived from these cells, in the presence of a drug, but not in its absence, can be detected using a sensitive assay. Detection of the drug-dependent antibodies permits diagnosis of cytopenia mediated by the drug. The method is applicable to a wide variety of drugs. Flow cytom. histograms for e.g. detection of probenecid-dependent antibodies that bind red blood cells are included, and mean 142platelet immunofluorescence values obtained in studies with drug-induced antibodies are tabulated.

L9 ANSWER 201 OF 454 CA COPYRIGHT 1998 ACS
AN 122:281940 CA
TI Effects of simvastatin on liver and plasma levels of cholesterol, dolichol and ubiquinol in hypercholesterolemic rats
AU Marinari, U. M.; Pronzato, M. A.; Dapino, D.; Gazzo, P.; Traverso, N.; Cottalasso, D.; Odetti, P.
CS Istituto di Patologia Generale, Universita di Genova, Genoa, Italy
SO Ital. J. Biochem. (1995), 44(1), 1-9
CODEN: IJBIAC; ISSN: 0021-2938
DT Journal
LA English
AB Increased levels of blood cholesterol are considered as a major

factor in the development of atherosclerosis. Simvastatin, a drug which blocks hydroxymethylglutaryl CoA reductase (HMGCoAR), reduces plasma cholesterol and increases HDL-cholesterol in rats fed a hypercholesterolemic diet. Moreover, simvastatin produces a significant decrease of ubiquinol and dolichol and plasma and in liver.

L9 ANSWER 202 OF 454 CA COPYRIGHT 1998 ACS
AN 122:281927 CA
TI Effects of simvastatin on plasma lipoprotein subfractions, cholesterol esterification rate, and cholesteryl ester transfer protein in type II hyperlipoproteinemia
AU Homma, Yasuhiko; Ozawa, Hideki; Kobayashi, Toshio; Yamaguchi, Hiroshi; Sakane, Hiroya; Nakamura, Haruo
CS Department of Internal Medicine, Tokai University Oiso Hospital, 21-1, Gakkyo, Oiso, 259-01, Japan
SO Atherosclerosis (Shannon, Irel.) (1995), 114(2), 223-34
CODEN: ATHSBL; ISSN: 0021-9150
DT Journal
LA English
AB We investigated the effects of simvastatin on plasma levels of lipoprotein subfractions, cholesterol esterification rates and activities of cholesteryl ester transfer protein (CETP) in 28 patients with type II hyperlipoproteinemia (i.e., nonfamilial hyperlipoproteinemia type IIa and type IIb, and heterozygous familial hypercholesterolemia (FH)). Plasma levels of VLDL-cholesterol (C) and VLDL-triglyceride (TG) were significantly reduced overall by 12.9% and 4.2% resp., but not in FH. Plasma levels of intermediate-d. lipoprotein cholesterol (IDL-C) and IDL-TG were decreased overall by 23.2% and 12.3%, resp., again mainly due to decreases seen in nonfamilial type II hyperlipoproteinemia. Plasma levels of LDL1 ($1.019 < d < 1.045$)-C and LDL1-TG were significantly reduced by 33.1% and 23.3%, resp. Plasma levels of LDL2 ($1.045 < d < 1.063$)-C were significantly reduced by 22.9% overall but not in FH. Gradient PAGE showed no consistent changes in the distribution of LDL particles. Thus, plasma levels of all apo B-contg. lipoprotein subfractions were reduced by simvastatin, but its effects varied among the three subgroups. Cholesterol esterification rates were suppressed by 9.3% and activities of cholesteryl ester transfer protein were reduced by 30.6%. Changes in CETP activity and in plasma levels of cholesterol in lipoprotein subfractions were not correlated. Thus, the changes in distribution of lipoprotein subfractions were not due mainly to CETP suppression.

L9 ANSWER 203 OF 454 CA COPYRIGHT 1998 ACS
AN 122:281249 CA
TI Quantitation of simvastatin and its .beta.-hydroxyacid metabolite in plasma by HPLC with API-CI tandem MS
AU Gilbert, J. D.; Olah, T. V.; Morris, M. J.; Schwartz, M. S.; McLoughlin, D. A.
CS Merck Research Laboratories, West Point, PA, 19486, USA
SO Methodol. Surv. Bioanal. Drugs (1994), 23(Biofluid and Tissue Analysis for Drugs, Including Hypolipidaemics), 157-67
CODEN: MSBDE6
DT Journal
LA English
AB A method based on LC-MS-MS has been developed for the assay in plasma of simvastatin and its .beta.-hydroxyacid metabolite, which are sep. isolated by SPE. After hydrolysis of the lactone, both intrinsic and generated acid are esterified with PFB bromide and chromatographed on a 5 cm C-18 column interfaced to a triple quadrupole mass spectrometer for MRM-mode detection by API-CI. The technique's very high specificity permits a chromatog. run time of 3

min. The method has a lower quantifiable limit of 0.5 ng/mL with inter- and intra-day C.V.s <10%, and has served for assaying plasma from dosed dogs and human volunteers.

L9 ANSWER 204 OF 454 CA COPYRIGHT 1998 ACS
AN 122:230793 CA
TI Prevention and treatment of Alzheimer's disease with HMG-CoA reductase inhibitors
IN Scolnick, Edward M.
PA Merck and Co., Inc., USA
SO PCT Int. Appl., 31 pp.
CODEN: PIXXD2
PI WO 9506470 A1 950309
DS W: AU, BB, BG, BR, BY, CA, CN, CZ, FI, GE, HU, JP, KE, KG, KR, KZ, LK, LT, LV, MD, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SI, SK, TJ, TT, UA, US, US, UZ
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG
AI WO 94-US7518 940705
PRAI US 93-113880 930830
US 93-114270 930830
DT Patent
LA English
OS MARPAT 122:230793
AB The present invention relates to the administration of an HMG-CoA reductase inhibitor, including lovastatin and simvastatin, the open-ring dihydroxy acid forms thereof, and salts and esters thereof, and pravastatin and fluvastatin, the closed ring lactone forms and salts and esters thereof, to humans to lower Apolipoprotein E isoform 4 (ApoE isoform 4) levels in the central nervous system to treat, arrest the development of and prevent the onset of Alzheimer's disease. Thus, effects of HMG-CoA reductase inhibitors on cerebrospinal fluid levels of ApoE in Alzheimer's patients homozygous for Apo E type 4 alle were studied.

L9 ANSWER 205 OF 454 CA COPYRIGHT 1998 ACS
AN 122:230516 CA
TI Effects of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors on mitochondrial respiration in ischemic rat hearts
AU Satoh, Kumi; Ichihara, Kazuo
CS Department of Pharmacology, Hokkaido College of Pharmacy, 7-1 Katsuraoka, Otaru, 047-02, Japan
SO Eur. J. Pharmacol., Environ. Toxicol. Pharmacol. Sect. (1995), 292(3-4), 271-5
CODEN: EPEPEG; ISSN: 0926-6917
DT Journal
LA English
AB The aim of the present study was to examine the effects of 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) reductase inhibitors on mitochondrial respiration in ischemic rat hearts, and to compare the effects between water-sol. pravastatin and lipid-sol. simvastatin. Either vehicle (0.5% CM-cellulose), pravastatin (2 or 4 mg/kg per day), or simvastatin (1 or 2 mg/kg per day) was orally administered for 3 wk. Ischemia was induced by ligating the aorta for 60 min in anesthetized open chest rats under artificial respiration. The hearts were removed, mitochondria were isolated, and the respiration was detd. by polarog. using glutamate and succinate as substrates. When succinate was used as a substrate, the ADP-stimulated respiration (QO3) and ATP prodn. per unit oxygen (ADP/O ratio) were decreased by ischemia. The decreases in QO3 and ADP/O ratio in the pravastatin- and simvastatin-treated groups appeared to be more prominent than those in the vehicle-treated group. This was esp. true in the simvastatin-treated group. The ADP-limited respiration

(QO4) with succinate in the vehicle-treated heart was slightly increased by ischemia, while that in the pravastatin- or simvastatin-treated hearts was decreased. In conclusion, HMG-CoA reductase inhibitors may result in worsening of myocardial mitochondrial respiration during ischemia.

=> s l4

L10 147 L4

=> d l10 200-205 bib,ab

147 ANSWERS ARE AVAILABLE. SPECIFIED ANSWER NUMBER EXCEEDS ANSWER SET SIZE
The answer numbers requested are not in the answer set.
ENTER ANSWER NUMBER OR RANGE (1):50-55

L10 ANSWER 50 OF 147 CA COPYRIGHT 1998 ACS
AN 126:218 CA
TI Clinical pharmacokinetics of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors
AU Desager, Jean-Pierre; Horsmans, Yves
CS Departement de Medecine Interne, Universite Catholique de Louvain, Brussels, Belg.
SO Clin. Pharmacokinet. (1996), 31(5), 348-371
CODEN: CPKNDH; ISSN: 0312-5963
PB Adis
DT Journal; General Review
LA English
AB A review with 150 refs. 3-Hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase is the key enzyme of cholesterol synthesis. HMG-CoA reductase inhibitors are potent reversible inhibitors of this enzyme, which act by competing for the substrate HMG-CoA. This review is mainly devoted to the 4 main HMG-CoA reductase inhibitors used today: lovastatin, simvastatin, pravastatin and fluvastatin. Depending upon the dosage, these drugs are able to reduce plasma cholesterol levels by more than 40%. After absorption, each undergoes extensive hepatic first-pass metab. Greater than 5 primary metabolites are formed, some of which are active inhibitors. The elimination half-lives vary from 0.5 to 3.5 h and excretion is mainly via the feces. A limited no. of drug interactions has been reported. Increases in liver enzymes and muscle creatine kinase activity are among the most severe adverse effects. These powerful drugs should be reserved for patients with high plasma cholesterol levels and/or those with cardiovascular disease. New therapeutic approaches to atherosclerosis are currently under investigation. HMG-CoA reductase inhibitors are the cornerstone of this research.

L10 ANSWER 51 OF 147 CA COPYRIGHT 1998 ACS
AN 126:52 CA
TI A review of current clinical findings with fluvastatin
AU Garnett, William R.
CS Medical College Virginia, Virginia Commonwealth University, Richmond, VA, 23298-0533, USA
SO Am. J. Cardiol. (1996), 78(6A), 20-25
CODEN: AJCDAG; ISSN: 0002-9149
PB Excerpta Medica
DT Journal; General Review
LA English
AB A review with 18 refs. Fluvastatin, the newest member of the class of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibitors, is structurally different from the fungal metabolites (lovastatin,

pravastatin, and simvastatin) and is wholly synthetic. Fluvastatin has a distinct biopharmaceutical profile, including a short systemic exposure time (half-life of 1.2 h) and virtually no active circulating metabolites. Fluvastatin is targeted to the liver, where it is rapidly metabolized; 98% of fluvastatin is protein-bound. Double-blind, placebo-controlled studies have demonstrated that fluvastatin at daily dosages of 20-40 mg produces significant decreases from baseline in low-d. lipoprotein (LDL) cholesterol on the order of 22-31% in patients with severe primary hypercholesterolemia (mean baseline LDL cholesterol 227 mg/dL) and decreases of 19-25% in patients with familial hypercholesterolemia (mean baseline LDL cholesterol 270 mg/dL). Interim results of a titrate-to-goal, 20-wk study in patients with moderate hypercholesterolemia (LDL cholesterol .gtoreq.160 mg/dL and triglycerides .ltoreq.350 mg/dL) demonstrate that fluvastatin, 20 mg/day, lowers LDL cholesterol by 21% within 6 wk. Long-term results indicate that the lipid-lowering effects of fluvastatin are sustained for 96 wk. Further, one study has shown that the combination of low-dose fluvastatin plus niacin decreased LDL cholesterol levels 40% without untoward adverse events, suggesting that this combination is effective and safe for patients needing intensive lipid-lowering therapy. Asymptomatic, reversible increases in hepatic transaminase levels occur in fluvastatin-treated patients at a frequency comparable to that reported for other HMG-CoA reductase inhibitors. The 20-30% redn. in LDL cholesterol required by the majority of patients with hypercholesterolemia can be achieved with fluvastatin at 20 or 40 mg/day as well as with the other available HMG-CoA reductase inhibitors at their most commonly prescribed doses. Fluvastatin, priced 40% lower than other statins, provides the most cost-effective means of safely achieving goal LDL cholesterol levels in these patients.

L10 ANSWER 52 OF 147 CA COPYRIGHT 1998 ACS
AN 125:316921 CA
TI Efficacy and tolerability of fluvastatin and simvastatin in hypercholesterolemic patients: A double-blind, randomized, parallel-group comparison
AU Schulte, Karl-Ludwig; Beil, Stefan
CS Department Internal Medicine, University-Hospital Charite, Berlin, Germany
SO Clin. Drug Invest. (1996), 12(3), 119-126
CODEN: CDINFR; ISSN: 1173-2563
DT Journal
LA English
AB The efficacy and tolerability of simvastatin and fluvastatin were compared in a randomized, parallel-group study using marketed formulations of the drugs and identical encapsulation to ensure blindness. 120 Patients with primary hypercholesterolemia (LDL > 185 mg/dL), who entered a run-in, washout period of 4 wk (3 mo in the case of previous statin treatment), were randomized to fluvastatin 40mg or simvastatin 20mg once daily in the evening. After 4 wk, the doses were doubled (80 and 40mg once daily in the evening, resp.) in all patients for another 6 wk. There were no significant differences between the 2 groups at randomization. Mean LDL-C fell by 24% by the end of the first 4 wk on fluvastatin 40mg once daily and by 31% after another 6 wk on 80mg once daily. The corresponding decreases on simvastatin were 24 and 34%. The difference between the treatment groups in total cholesterol and triglycerides, HDL-C and LDL-C, were not significant. At the end of the study, there was a pos. correlation between baseline LDL-C and percentage LDL-C redn. in the fluvastatin group ($p < 0.001$) but not in the simvastatin group ($p = 0.752$). From the lowest (<200 mg/dL)

to the middle two (200 to 237 mg/dL) and to the highest (>237 mg/dL) quartile of baseline LDL-C, fluvastatin reduced LDL-C by 16, 31 and 43%, resp. The corresponding figures for simvastatin were 37, 33 and 35%. Adverse events occurred in 18 patients on fluvastatin and in 28 patients on simvastatin treatment. In the simvastatin group, a causal relationship between adverse event and study drug was regarded as likely in 4 cases, but in no case for patients receiving fluvastatin. There were statistically, but not clin., relevant increases in aminotransferases (ASAT and ALAT) and creatine kinase (CK) in both groups. The mean increases in ASAT and ALAT were about 42 and 55% on simvastatin and 34 and 27% on fluvastatin, resp. The mean CK levels increased during simvastatin and fluvastatin treatments by about 35 and 18%, resp. Fluvastatin and simvastatin induced indistinguishable redns. in LDL-C on their highest and next-highest recommended doses. The potency ratio was 1:2 (fluvastatin:simvastatin). Both drugs were well tolerated, with no significant difference in the incidence of drug-related adverse events.

L10 ANSWER 53 OF 147 CA COPYRIGHT 1998 ACS
AN 125:316905 CA
TI A comparison of the tolerability and efficacy of lovastatin 20 mg and fluvastatin 20 mg in the treatment of primary hypercholesterolemia
AU Berger, Marc L.; Wilson, Helene M.; Liss, Charles L.
CS Merck and Co., Inc., West Point, PA, 19486, USA
SO J. Cardiovasc. Pharmacol. Ther. (1996), 1(2), 101-105
CODEN: JCPTFE; ISSN: 1074-2484
DT Journal
LA English
AB To compare the cholesterol-lowering potency of fluvastatin and lovastatin, a randomized, prospective, open-label parallel study was conducted in patients eligible for drug therapy by National Cholesterol Education Program guidelines. The study was conducted at eight centers in the United States. Patients were required to follow a cholesterol-lowering diet and were withdrawn from all lipid-lowering agents for 4 wk prior to study entry. Patients were randomized to receive lovastatin 20 mg or fluvastatin 20 mg daily for 6 wk. The two treatment groups were comparable with respect to demog. and clin. characteristics. Baseline lipid levels in the two groups were comparable. Lovastatin was significantly more effective than fluvastatin in lowering total cholesterol (-19.5% vs. -12.8%) and low d. lipoprotein cholesterol (-27.6% vs. -18.2%). Changes in high-d. lipoprotein and triglyceride levels were comparable in the two groups. The differences in cholesterol lowering were similar in the three strata of coronary heart disease risk factor status as defined by the second NCEP Adult Treatment Panel. Both treatments were well tolerated. Across the three chronic heart disease risk strata, lovastatin appears to be significantly more potent than fluvastatin, on a per mg basis, in lowering cholesterol levels.

L10 ANSWER 54 OF 147 CA COPYRIGHT 1998 ACS
AN 125:316814 CA
TI Cost-effectiveness of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor therapy in the managed care era
AU Jacobson, Terry A.
CS School Medicine, Emory University, Atlanta, GA, 30303, USA
SO Am. J. Cardiol. (1996), 78(6A), 32-41
CODEN: AJCDAG; ISSN: 0002-9149
DT Journal
LA English
AB More than $100 billion is spent in the United States each year on cardiovascular disease, primarily for hospitalizations and

revascularization procedures. This is more than for any other disease state. As the clin. practice of medicine shifts from the paradigm of private practice to the managed care environment, cost-effectiveness is becoming increasingly important. A primary measure in analyzing cost-effectiveness is the cost-effectiveness ratio, or the dollar cost per unit of improvement for a given expenditure. This measure allows health-care planners to compare completely different interventions. With approx. 52 million adult U.S. citizens having elevated low-d. lipoprotein (LDL) cholesterol levels, lipid-lowering therapy-with diet or HMG-CoA reductase inhibitors-is an important consideration for primary care physicians and managed care providers. The National Health and Nutrition Examn. Survey (NHANES) III indicates that 75-88% of adults who have coronary artery disease (CAD) risk factors or CAD require only a moderate (20-30%) redn. in LDL cholesterol levels to reach National Cholesterol Education Program goals. The clin. literature shows that all 4 of the currently available HMG-CoA reductase inhibitors can provide appropriate, moderate LDL cholesterol redns. within their recommended dosage ranges. For the majority of patients who need a 20-30% redn. in LDL cholesterol, fluvastatin 20 or 40 mg once daily provides the most cost-effective HMG-CoA therapy, expressed as cost of therapy per 1% LDL cholesterol redn. For patients who need a >30% LDL cholesterol redn., a high-dose HMG-CoA reductase inhibitor (e.g., simvastatin 20 or 40 mg/day) or a combination of a lower-dose HMG-CoA reductase inhibitor and a bile acid resin is the preferred initial therapy. Although a true cost-effectiveness anal. would incorporate morbidity and mortality data from clin. trials, anal. using intermediate endpoints, such as LDL cholesterol redn., suggests that fluvastatin is the preferred initial HMG-CoA reductase inhibitor for the treatment of moderate hyperlipidemia.

L10 ANSWER 55 OF 147 CA COPYRIGHT 1998 ACS
AN 125:315863 CA
TI Myopathy associated with lipid lowering therapy in patients with previously undiagnosed or undertreated hypothyroidism
AU Lang, James E.; Wang, Ping; Glueck, C. J.
CS Cholesterol Center, Jewish Hospital, Cincinnati, OH, 45229, USA
SO Clin. Chim. Acta (1996), 254(1), 85-92
CODEN: CCATAR; ISSN: 0009-8981
DT Journal; General Review
LA English
AB A review with .apprx.14 refs.

=> s l5

L11 7 L5

=> d l11 1-7 bib,ab

L11 ANSWER 1 OF 7 CA COPYRIGHT 1998 ACS
AN 125:308702 CA
TI Use of HMG-coenzyme A reductase inhibitors as antiaging agents
IN Breton, Lionel; de Lacharriere, Olivier
PA Oreal S. A., Fr.
SO Eur. Pat. Appl., 8 pp.
CODEN: EPXXDW
PI EP 738510 A2 961023
DS R: DE, ES, FR, GB, IT
AI EP 96-400697 960329
PRAI FR 95-4747 950420
DT Patent
LA French

AB HMG-CoA reductase inhibitors are used as antiaging agents. These compns. are also used as skin whitening and antiwrinkle compns. A cosmetic gel contained fluvastatin 0.005, hydroxypropyl cellulose 1.0, antioxidant 0.05, isopropanol 40.0, preservative 0.3, and water q.s. 100%.

L11 ANSWER 2 OF 7 CA COPYRIGHT 1998 ACS
AN 122:229991 CA
TI The determination of a HMG-CoA reductase inhibitor, dalvastatin, in human plasma by HPLC linked to MS-MS
AU Hsu, Shih-Hsien; Schlater, Terri; Rich, Lisa
CS Department Clinical Drug Disposition, Rhone-Poulenc Rorer Central Research, Collegeville, PA, 19426, USA
SO Methodol. Surv. Bioanal. Drugs (1994), 23(Biofluid and Tissue Analysis for Drugs, Including Hypolipidaemics), 169-76
CODEN: MSBDE6
DT Journal
LA English
AB A method was developed for the detn., in human blood plasma, of dalvastatin as its lactone and its active form, the acid. The lactone, acid and the internal std. (simvastatin) were extd. from buffered plasma by using C18 SPE columns. Anal. sepn. was performed with a C8 high-speed column using acidified aq. acetonitrile as eluent. Tandem-MS was used for detection and for quantification, which embraced the range 0.2-100 ng/mL with a 1-mL plasma sample; recoveries were 70-80%. The method has served well for several clin. pharmacokinetic studies.

L11 ANSWER 3 OF 7 CA COPYRIGHT 1998 ACS
AN 121:238511 CA
TI Separation of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor drug substance diastereomers and their analogs on .beta.-cyclodextrin stationary phase
AU Kumar, Narendra; Windisch, Vincent; Trivedi, Pravin; Golebiowski, Chris
CS Department of Analytical and Physical Chemistry, Rhone-Poulenc Rorer Central Research, 500 Arcola Road, P.O. Box 1200, Collegeville, PA, 19426-0107, USA
SO J. Chromatogr., A (1994), 678(2), 259-63
CODEN: JCRAEY
DT Journal
LA English
AB .beta.-Cyclodextrin stationary phases are extremely useful in the sepn. of complex diastereomeric mixts. under normal-phase chromatog. conditions. The retention behavior of the 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase inhibitors is influenced by the size and chain length of the polar alc. modifier. Retention time changes caused by different alc. modifiers can be explained by hydrogen bonding and steric effects involving the stationary phase, the analyte and the alc. modifier.

L11 ANSWER 4 OF 7 CA COPYRIGHT 1998 ACS
AN 121:125253 CA
TI Use of coenzyme Q10 in combination with HMG-CoA reductase inhibitor therapies
IN Folkers, Karl A.; Langsjoen, Per H.; Willis, Richard A.
PA Karl Folkers Foundation for Biomedical and Clinical Research, USA
SO U.S., 11 pp. Cont.-in-part of U.S. 5,082,650.
CODEN: USXXAM
PI US 5316765 A 940531
AI US 91-762312 910919
PRAI US 89-404228 890907
DT Patent

LA English
AB Methods are diclosed for inhibiting the side effects attendant treatment with HMG-CoA reductase inhibitors. Treatment of a patient with an HMG-CoA reductase inhibitor in combination with coenzyme Q10 provides a redn. in patient cholesterol levels and guards against typical HMG-CoA reductase inhibitor side effects, most notably liver dysfunction and cardiac dysfunction. The combination of lovastatin, an HMG-CoA reductase inhibitor, and coenzyme Q10 in ratios of between 1:2 to 1:29 provide significant enhancement of a patient's cardiac condition. Other HMG-CoA reductase inhibitors which may be included in the claimed combinations include pravastatin, compactin, fluvastatin, dalvastatin, simvastatin, etc. Case summaries and data are included. In animal studies, lovastatin and pravastatin lowered coenzyme Q10 serum concns.

L11 ANSWER 5 OF 7 CA COPYRIGHT 1998 ACS
AN 120:143840 CA
TI Epimerization and hydrolysis of dalvastatin, a new hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitor
AU Won, Chong Min
CS Anal. Phys. Chem. Dep., Rhone-Poulenc Rorer Cent. Res., Collegeville, PA, 19426-0107, USA
SO Pharm. Res. (1994), 11(1), 165-70
CODEN: PHREEB; ISSN: 0724-8741
DT Journal
LA English
AB In aq. solns., dalvastatin (I) undergoes epimerization as well as hydrolysis. The transformation of I was studied as a function of pH at 25.degree. in aq. solns. contg. 20% MeCN. At all pH values, 1st-order plots for the conversion are biphasic, indicating rapid equilibration of I with its epimer and slower hydrolysis of I to the corresponding .beta.-hydroxy acid (II). Apparent 1st-order rate consts. for the biexponential equation are given as a function of pH. The alkyl-oxygen cleavage of the lactone ring results in the epimerization of I, whereas the acyl-oxygen cleavage results in the hydrolysis of I to II. The epimerization is an SN1 reaction. The epimerization rate increased with an increase in the water content of the solvent. The hydrolysis of I was acid and base catalyzed. The hydrolysis was reversible in acidic media and irreversible in neutral and basic media. At pH values >9, the hydrolysis reaction proceeded more rapidly than the epimerization.

L11 ANSWER 6 OF 7 CA COPYRIGHT 1998 ACS
AN 118:52213 CA
TI RG 12561 (dalvastatin): a novel synthetic inhibitor of HMG-CoA reductase and cholesterol-lowering agent
AU Amin, Dilip; Gustafson, Susan K.; Weinacht, Judith M.; Cornell, Susan A.; Neuenschwander, Kent; Kosmider, Benedict; Scotese, Anthony C.; Regan, John R.; Perrone, Mark H.
CS Dep. Cardiovas. Biol., Rhone-Poulenc Rorer Cent. Res., Collegeville, PA, USA
SO Pharmacology (1993), 46(1), 13-22
CODEN: PHMGBN; ISSN: 0031-7012
DT Journal
LA English
AB RG 12561 (dalvastatin, I) is a prodrug which converts to its open hydroxyacid form in the body. The Na salt of I (RG 12561-Na) is a potent inhibitor of 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase, the rate-limiting enzyme in the cholesterol biosynthetic pathway. It competitively inhibits rat liver HMG-CoA reductase with an IC50 value of 3.4 nmol/L. In the same assay, the IC50 values for other potent HMG-CoA reductase inhibitors, lovastatin-Na and pravastatin, were 2.3 and 8.9 nmol/L, resp. In Hep G2 liver cells,

RG 12561-Na, lovastatin-Na and pravastatin inhibited cholesterol biosynthesis from radiolabeled octanoate with IC50 values of 4 and 5 nmol/L and 1.1 .mu.mol/L, resp. In a rat ex vivo assay, orally administered I, lovastatin and pravastatin inhibited cholesterol biosynthesis in liver slices with ED50 values of 0.9, 0.5 and 12 mg/kg, resp. In cholestyramine-fed hamsters, I (0.1% in food for 18 days) reduced LDL cholesterol, whereas HDL was slightly increased. The redns. in the LDL/HDL ratio for I, RG 12561-Na, lovastatin and lovastatin-Na were 35, 76, 88 and 88%, resp. At a higher dose, I (0.4% in food) reduced serum cholesterol, LDL and LDL/HDL by 84, 97 and 91%, resp. In WHHL rabbits, I and lovastatin (5 mg/kg, twice daily, 12 days) reduced serum cholesterol by 17 and 16%, resp. These results demonstrate that RG 12561 is a potent cholesterol-lowering agent.

L11 ANSWER 7 OF 7 CA COPYRIGHT 1998 ACS
AN 117:37258 CA
TI Structure of RG-12561 dichloromethane solvate and a diastereomer
AU Ammon, Herman L.; Prasad, Satya M.; Kumar, N.
CS Dep. Chem. Biochem., Univ. Maryland, College Park, MD, 20742, USA
SO Acta Crystallogr., Sect. C: Cryst. Struct. Commun. (1992), C48(4), 669-75
CODEN: ACSCEE; ISSN: 0108-2701
DT Journal
LA English
AB [4.alpha.,6.beta.(E)](.+-.)-6-{2-[2-(4-Fluoro-3-methylphenyl)-4,4,6,6-tetramethyl-1-cyclohexen-1-yl]ethenyl}-4-hydroxytetrahydropyran-2-one (RG-12561) dichloromethane solvate (2:1) (I) is triclinic, space group P.hivin.1, with a 11.7413(5), b 13.0279(5), c 16.2332(9) .ANG., .alpha. 99.456(4), .beta. 94.217(4), and .gamma. 101.893(4).degree.; dc = 1.195 for Z = 2 (2 mols./Z); final R = 0.053; Rw = 0.060 for 4031 reflections. [4.beta.,6.alpha.(E)]-(.+-.)-6-{2-[2-(4-Fluoro-3-methylphenyl)-4,4,6,6-tetramethyl-1-cyclohexen-1-yl]ethenyl}-4-hydroxytetrahydropyran-2-one (II) is triclinic, space group P.hivin.1, with a 6.054(2), b 12.931(2), c 14.838(3) .ANG., .alpha. 67.70(2), .beta. 85.75(2), and .gamma. 82.85(2).degree.; dc = 1.203 for Z = 2; final R = 0.073; Rw = 0.081 for 1588 reflections. The at. coordinates are given. I is a potent HMG-CoA reductase inhibitor and has the potential to function as a superior hypocholesterolemic agent; II lacks this activity. I and II have different conformations and mol.-model calcns. suggest that crystal-packing effects are primarily responsible for the overall conformation of II. The principal intermol. contacts are H bonds of the type O-H...O:C.

=> s l6

L12 313 L6

=> d l12 50-56 bib,ab

L12 ANSWER 50 OF 313 CA COPYRIGHT 1998 ACS
AN 122:80953 CA
TI Enantioselective synthesis of the hexahydronaphthalene nucleus of (-)-compactin from ethyl (1R,2S)-2-methyl-4-oxocyclohexanecarboxylate and 2-(3-nitropropyl)-1,3-dioxolane as four carbon bifunctional annelating agent
AU Barco, Achille; Benetti, Simonetta; Bianchi, Anna; Casolari, Alberto; Pollini, Gian P.; Romagnoli, Romeo; Spalluto, Giampiero; Zanirato, Vinicio
CS Dip. Chimica, Ferrara, I-44100, UK

SO Tetrahedron (1994), 50(40), 11743-54
CODEN: TETRAB; ISSN: 0040-4020
DT Journal
LA English
AB An enantioselective approach to the synthesis of the hexahydronaphthalene nucleus of natural compactin is described. The key elements of the synthesis are the prepn. of the chiral starting material through enzymic resoln. of the readily available cis 2-methyl-4-oxocyclohexanecarboxylic acid, conversion into the suitably protected (4S,5S)-4-hydroxymethyl-5-methyl-2-cyclohexen-2-one by regioselective introduction of the .alpha.,.beta.-carbon-carbon double bond by Pd(II)-catalyzed dehydrosilylation, construction of the new six-membered ring onto the preexisting carbon skeleton using 2-(3-nitropropyl)-1,3-dioxolane as a four carbon bifunctional annelating reagent, elaboration of the derived hexahydronaphthalenone to an advanced precursor already taken to the natural target by functional group manipulation, including conversion of the nitro group to the oxygenated functions at C-1 and dehydration of an allylic alc. precursor to the required 1,3-diene moiety.

L12 ANSWER 51 OF 313 CA COPYRIGHT 1998 ACS
AN 122:48119 CA
TI Saccharomyces cerevisiae YDR1, which encodes a member of the ATP-binding cassette (ABC) superfamily, is required for multidrug resistance
AU Hirata, Dai; Yano, Kiichiro; Miyahara, Kohji; Miyakawa, Tokichi
CS Dep. Fermentation Technology, Hiroshima Univ., Higashi-Hiroshima, 724, Japan
SO Curr. Genet. (1994), 26(4), 285-94
CODEN: CUGED5; ISSN: 0172-8083
DT Journal
LA English
AB A multidrug resistance gene, YDR1, of Saccharomyces cerevisiae, which encodes a 170-kDa protein of a member of the ABC superfamily, was identified. Disruption of YDR1 resulted in hypersensitivity to cycloheximide, cerulenin, compactin, staurosporine and fluphenazine, indicating that YDR1 is an important determinant of cross resistance to apparently-unrelated drugs. The Ydr1 protein bears the highest similarity to the S. cerevisiae Snq2 protein required for resistance to the mutagen 4-NQO. The drug-specificity anal. of YDR1 and SNQ2 by gene disruption, and its phenotypic suppression by the overexpressed genes, revealed overlapping, yet distinct, specificities. YDR1 was responsible for cycloheximide, cerulenin and compactin resistance, whereas, SNQ2 was responsible for 4-NQO resistance. The two genes had overlapping specificities toward staurosporine and fluphenazine. The transcription of YDR1 and SNQ2 was induced by various drugs, both relevant and irrelevant to the resistance caused by the gene, suggesting that drug specificity can be mainly attributed to the functional difference of the putative transporters. The transcription of these genes was also increased by heat shock. The yeast drug-resistance system provides a novel model for mammalian multidrug resistance.

L12 ANSWER 52 OF 313 CA COPYRIGHT 1998 ACS
AN 122:23365 CA
TI Induction of normal phenotypes and potentiation of 5-fluorouracil by an HMG-CoA reductase inhibitor, compactin, in ras-transformed cells
AU Matsuda, N.; Kageyama, S.; Endo, A.; Umezawa, K.
CS Dep. Applied Chemistry, Keio University, Yokohama, 223, Japan
SO Cell. Pharmacol. (1994), 1(5), 219-23
CODEN: CEPHEG
DT Journal

LA English
AB Compactin, an inhibitor of 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase, induced normal phenotypes in K-rasts-NRK cells. It also induced actin stress fiber organization and fibronectin expression in K-rasts-NRK cells. Compactin inhibited the growth of ras-transformed cells more strongly than their normal counterpart cells. Compactin did not potentiate the growth inhibitory effect of 5-fluorouracil (5-FU) on K-ras-NRK cells when added simultaneously. However, when the cells were pretreated with compactin for 48 h, compactin potentiated the antiproliferative effect of 5-FU.

L12 ANSWER 53 OF 313 CA COPYRIGHT 1998 ACS
AN 122:1102 CA
TI Method and compositions for disrupting the epithelial barrier function
IN Elias, Peter M.; Thornfeldt, Carl R.; Grayson, Stephen
PA Cellegy Pharmaceuticals, Inc., USA; Regents of the University of California
SO PCT Int. Appl., 64 pp.
CODEN: PIXXD2
PI WO 9421230 A1 940929
DS W: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KG, KP, KR, KZ, LK, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG
AI WO 94-US3030 940321
PRAI US 93-33807 930319
DT Patent
LA English
AB This invention relates generally to a novel method for enhancing penetration of physiol. active substances for cutaneous or transdermal delivery through epithelium which comprises the stratum corneum/epidermis and keratinizing mucous membranes. More specifically, it relates to a method and compn. for disrupting the epithelial barrier function in a host by applying to the epithelium a barrier-disrupting amt. of at least one agent selected from the group consisting of an inhibitor of ceramide synthesis, an inhibitor of acylceramide synthesis, an inhibitor of glucosylceramide synthesis, an inhibitor of sphingomyelin synthesis, an inhibitor of fatty acid synthesis, an inhibitor of cholesterol synthesis, a degrdn. enzyme of ceramides, acylceramide, glucosylceramides, sphingomyelin, an inhibitor of phospholipid, glycosphingolipid, including glucosylceramide, acylceramide or sphingomyelin degrdn., and both inhibitors and stimulators of metabolic enzymes of free fatty acids, ceramide, and cholesterol.

L12 ANSWER 54 OF 313 CA COPYRIGHT 1998 ACS
AN 121:133826 CA
TI Titanium-induced dicarbonyl coupling and the chemical degradation of mevinolin and compactin
AU Zhang, Chengzhi
CS Univ. Alberta, Edmonton, AB, Can.
SO (1993) 278 pp. Avail.: NLC Order No. DANN82127
From: Diss. Abstr. Int. B 1994, 54(9),4683
DT Dissertation
LA English
AB Unavailable

L12 ANSWER 55 OF 313 CA COPYRIGHT 1998 ACS
AN 121:125253 CA
TI Use of coenzyme Q10 in combination with HMG-CoA reductase inhibitor therapies

IN Folkers, Karl A.; Langsjoen, Per H.; Willis, Richard A.
PA Karl Folkers Foundation for Biomedical and Clinical Research, USA
SO U.S., 11 pp. Cont.-in-part of U.S. 5,082,650.
CODEN: USXXAM
PI US 5316765 A 940531
AI US 91-762312 910919
PRAI US 89-404228 890907
DT Patent
LA English
AB Methods are diclosed for inhibiting the side effects attendant treatment with HMG-CoA reductase inhibitors. Treatment of a patient with an HMG-CoA reductase inhibitor in combination with coenzyme Q10 provides a redn. in patient cholesterol levels and guards against typical HMG-CoA reductase inhibitor side effects, most notably liver dysfunction and cardiac dysfunction. The combination of lovastatin, an HMG-CoA reductase inhibitor, and coenzyme Q10 in ratios of between 1:2 to 1:29 provide significant enhancement of a patient's cardiac condition. Other HMG-CoA reductase inhibitors which may be included in the claimed combinations include pravastatin, compactin, fluvastatin, dalvastatin, simvastatin, etc. Case summaries and data are included. In animal studies, lovastatin and pravastatin lowered coenzyme Q10 serum concns.

L12 ANSWER 56 OF 313 CA COPYRIGHT 1998 ACS
AN 121:82875 CA
TI Preparation of octahydronaphthalenone oxime derivatives for cholesterol biosynthesis inhibition.
IN Kogen, Hiroshi; Koga, Teiichiro; Komai, Toru; Iwabuchi, Haruo; Kurabayashi, Masaaki
PA Sankyo Co., Ltd., Japan
SO Eur. Pat. Appl., 97 pp.
CODEN: EPXXDW
PI EP 570245 A2 931118
DS R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE
AI EP 93-303757 930514
PRAI JP 92-122476 920515
DT Patent
LA English
OS MARPAT 121:82875
AB Title compds. [I; R = H, Me, OH; X = (substituted) alkyl, alkenyl, cycloalkyl, aryl, carbocyclic aryl-group substituted aralkyl, heterocyclic group; A = bond, alkylene, alkenylene, alkynylene, alkadienylene; Y = H, (substituted) aryl, cycloalkyl, heterocyclyl; and pharmaceutically acceptable salts and esters thereof], were prepd. Thus, title compd. II [prepn. from [2-[5-benzyloxyimino-2-methyl-8-(2-methylbutyryloxy)-3-oxo-1,2,3,5,6,7,8,8a-octahydro-1-naphthyl]ethyl]-4-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one given] inhibited HMG-CoA with IC50 = 16.3 nM.

=> log y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	68.45	98.92

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-17.02	-17.02

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=> file ificdb

COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                                0.15       0.15

FILE 'IFICDB' ENTERED AT 10:23:30 ON 28 JAN 1998
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FILE LAST UPDATED: 23 Jan 1998 (19980123/ED)
HIGHEST PATENT NUMBER: US5711025
UNITERM INDEXING LAST UPDATED: 21 Jan 1998 (19980121/UP)
INDEXING CURRENT THROUGH PAT PUB DATE: 30 Sep 1997 (19970930/PD)

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=> s 05860/un

05860 VASODILATION
L1         2482 05860/UN

=> s 05858/un

05858 VASCULAR SYSTEMS
L2         1435 05858/UN

=> s 08423/un

08423 ENDOTHELIAL CELLS
L3          389 08423/UN

=> s nitric oxide synthase or (NOS)

           8210 NITRIC
         106326 OXIDE
            358 SYNTHASE
             52 NITRIC OXIDE SYNTHASE
                  (NITRIC(W)OXIDE(W)SYNTHASE)
           1050 NOS
L4         1098 NITRIC OXIDE SYNTHASE OR (NOS)

=> s arginine

L5         1955 ARGININE
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=> s (lovastatin or pravastatin or simvastatin or fluvastatin or dalvastatin
or compactin)

            63 LOVASTATIN
            44 PRAVASTATIN
            37 SIMVASTATIN
            15 FLUVASTATIN
             2 DALVASTATIN
            15 COMPACTIN
L6          95 (LOVASTATIN OR PRAVASTATIN OR SIMVASTATIN OR FLUVASTATIN
               OR DALVASTATIN OR COMPACTIN)

=> d his


     (FILE 'HOME' ENTERED AT 10:23:20 ON 28 JAN 1998)

     FILE 'IFICDB' ENTERED AT 10:23:30 ON 28 JAN 1998
L1         2482 S 05860/UN
L2         1435 S 05858/UN
L3          389 S 08423/UN
L4         1098 S NITRIC OXIDE SYNTHASE OR (NOS)
L5         1955 S ARGININE
L6           95 S (LOVASTATIN OR PRAVASTATIN OR SIMVASTATIN OR FLUVASTATI

=> s 514565000/ncl

L7         157 514565000/NCL

=> s 514564000/ncl

L8         247 514564000/NCL

=> s l8 or l7

L9         356 L8 OR L7

=> s l1 and l4

L10          7 L1 AND L4

=> s l1 and l5

L11         29 L1 AND L5

=> s l5 and l6

L12          4 L5 AND L6

=> s l4 and l5

L13         46 L4 AND L5

=> s l6 and l13

L14          0 L6 AND L13

=> s l13 and l1

L15          2 L13 AND L1

=> s l10 or l12 or l15
```

L16 11 L10 OR L12 OR L15

=> s l9 or l1

L17 2828 L9 OR L1

=> s l9 and l1

L18 10 L9 AND L1

=> s l4 and l9

L19 23 L4 AND L9

=> s l5 and l9

L20 86 L5 AND L9

=> s l6 and l20

L21 0 L6 AND L20

=> s l4 and l20

L22 19 L4 AND L20

=> s l16 or l18

L23 19 L16 OR L18

=> s l22 or l23

L24 36 L22 OR L23

=> d l23 1-19 bib,ab

L23 ANSWER 1 OF 19 IFICDB COPYRIGHT 1998 IFI
AN 2859202 IFIPAT;IFIUDB;IFICDB
TI COMBINED USE OF ANGIOTENSIN INHIBITORS AND NITRIC OXIDE STIMULATORS TO TREAT FIBROSIS
INF Brecher, Peter, West Newton, MA
Chobanian, Aram, Natick, MA
IN Brecher Peter; Chobanian Aram
PAF Trustees of Boston University, Boston, MA
PA Boston University (1308)
EXNAM Hulina, Amy
AG Baker & Botts, LLP
PI US 5645839 970708
AI US 95-482819 950607
FI US 5645839 970708
DT UTILITY
FS CHEMICAL
CLMN 9
AB This invention pertains to the use of a combination of angiotensin inhibitors and nitric oxide stimulators to slow and reverse the process of fibrosis in the body. This combination of medicaments is particularly useful in the treatment of a variety of cardiovascular fibrotic pathologies, such as that associated with left ventricular hypertrophy secondary to hypertension, myocardial infarction, and myocarditis.

L23 ANSWER 2 OF 19 IFICDB COPYRIGHT 1998 IFI

AN 2803410 IFIPAT;IFIUDB;IFICDB
TI NITROSYLATION OF PROTEIN SH GROUPS AND AMINO ACID RESIDUES AS A THERAPEUTIC MODALITY
INF Loscalzo, Joseph, Dedham, MA
Simon, Daniel, Waban, MA
Singel, David, Arlington, MA
Stamler, Jonathan, Boston, MA
IN Loscalzo Joseph; Simon Daniel; Singel David; Stamler Jonathan
PAF Brigham and Women's Hospital, Boston, MA
PA Brigham and Women's Hospital (8822)
EXNAM Lilling, Herbert J
AG Herron, Charles J
Olstein, Elliot M
PI US 5593876 970114
AI US 94-287830 940809
RLI US 91-791668 911114 CONTINUATION-IN-PART ABANDONED
US 92-943835 920914 DIVISION ABANDONED
US 94-198854 940217 DIVISION
FI US 5593876 970114
DT UTILITY
FS CHEMICAL
CLMN 16
GI 41 Drawing Sheet; 51 Figures;
AB Nitrosylation of proteins and amino acid groups enables selective regulation of protein function, and also endows the proteins and amino acids with additional smooth muscle relaxant and platelet inhibitory capabilities. Thus, the invention relates to novel compounds achieved by nitrosylation of protein thiols. Such compounds include: S-nitroso-t-PA, S-nitroso-cathepsin; Snitroso-lipoprotein; and S-nitroso-immunoglobulin. The invention also relates to therapeutic use of S-nitroso-protein compounds for regulating protein function, cellular metabolism and effecting vasodilation, platelet inhibition, relaxation of nonvascular smooth muscle, and increasing blood oxygen transport by hemoglobin and myoglobin. The compounds are also used to deliver nitric oxide in its most bioactive form in order to achieve the effects described above, or for in vitro nitrosylation of molecules present in the body. The invention also relates to the nitrosylation of oxygen, carbon and nitrogen moieties present on proteins and amino acids, and the use thereof to achieve the above physiological effects.

L23 ANSWER 3 OF 19 IFICDB COPYRIGHT 1998 IFI
AN 2791364 IFIPAT;IFIUDB;IFICDB
TI CONTROLLED RELEASE DRUG SUSPENSION DELIVERY DEVICE; POLYMER WHICH FORMS MICROSCOPIC GEL BEADS UPON HYDRATION IN CORE; IMPERMEABLE, INSOLUBLE COATING WITH CONTAINS APERTURES WHICH PROVIDE AREA FOR HYDRATION AND RELEASE OF GEL BEADS
INF Pipkin, James D, Lawrence, KS
Rork, Gerald S, Lawrence, KS
IN Pipkin James D; Rork Gerald S
PAF Merck & Co, Inc, Rahway, NJ
PA Merck & Co Inc (54136)
EXNAM Spear, James M
AG Bigley, Francis P
Daniel, Mark R
PI US 5582838 961210
AI US 94-363451 941222
FI US 5582838 961210
DT UTILITY
FS CHEMICAL
MRN 8002 MFN: 0211
CLMN 23
GI 4 Drawing Sheet; 6 Figures;

AB A device is disclosed for the controlled delivery of a beneficial agent, the device consisting of (i) a core comprising at least two layers, wherein at least one layer comprises a beneficial agent and a polymer which forms microscopic gel beads upon hydration and at least one layer which comprises a polymer which forms microscopic gel beads upon hydration; and (ii) an impermeable, insoluble coating which adheres to and surrounds the core and contains apertures which provide an area for the hydration and release of the microscopic gel beads.

L23 ANSWER 4 OF 19 IFICDB COPYRIGHT 1998 IFI
AN 2750233 IFIPAT;IFIUDB;IFICDB
TI PREVENTING CONVERSION OF CITRULLINE TO ARGININOSUCCINATE TO LIMIT PATHOLOGICAL NITRIC OXIDE OVERPRODUCTION; HYPOTENSIVE THERAPY
INF Griffith, Owen W, Milwaukee, WI
Gross, Steven S, New York, NY
IN Griffith Owen W; Gross Steven S
PAF The Medical College of Wisconsin Research Foundation, Inc, Milwaukee, WI
PA Medical College of Wisconsin The (5187)
EXNAM Jordan, Kimberly
PI US 5545625 960813
AI US 94-354585 941212
FI US 5545625 960813
DT UTILITY; REASSIGNED
FS CHEMICAL
CLMN 35
GI 5 Drawing Sheet; 5 Figures;
AB Administration of argininosuccinate synthetase activity reducing agents, e.g., argininosuccinate synthetase induction blocking agents (e.g., antibiotics that bind to DNA sequences present in the upstream regulatory region of the argininosuccinate synthetase gene, such as mithramycin) and argininosuccinate synthetase inhibitors (e.g., L-citrulline antagonists such as methyl citrulline and L-aspartate antagonists such as Daspartate) is useful to prevent or treat sepsis or cytokineinduced systemic hypotension, is useful in the treatment of sepsis or cytokine-induced systemic hypotension to restore vascular sensitivity to the effects of Alpha 1-adrenergic agonists, and is useful to suppress an immune response, e.g., in treating inflammation. In one embodiment, certain argininosuccinate synthetase activity reducing agents are used together with **arginine** antagonists to treat sepsis or cytokine induced hypotension.

L23 ANSWER 5 OF 19 IFICDB COPYRIGHT 1998 IFI
AN 2747811 IFIPAT;IFIUDB;IFICDB
TI METHOD AND FORMULATION OF STIMULATING NITRIC OXIDE SYNTHESIS; ADMINISTERING MIXTURE OF **ARGININE** AND VENOUS DILATOR UNTIL DESIRABLE STATE OF VASORELAXATION IS OBTAINED
INF Kaesemeyer, W H, 2433 McDowell St, August, GA, 30904
IN Kaesemeyer W H
PAF Unassigned
PA Unassigned Or Assigned To Individual (68000)
EXNAM Killos, Paul J
AG Pearne, Gordon, McCoy & Granger
PI US 5543430 960806
AI US 94-321051 941005
FI US 5543430 960806
DT UTILITY
FS CHEMICAL
CLMN 22
GI 5 Drawing Sheet; 5 Figures;

AB A therapeutic mixture comprising a mixture of L-**arginine** and an agonist of **nitric oxide synthase** , namely nitroglycerin, is disclosed for the treatment of diseases related to vasoconstriction, wherein the vasoconstriction is relieved by stimulating the constitutive form of **nitric oxide synthase** (cNOS) to produce native nitric oxide (NO). The native NO having superior beneficial effect when compared to exogenous NO produced by a L-**arginine** independent pathway in terms of the ability to reduce clinical endpoints and mortality.

L23 ANSWER 6 OF 19 IFICDB COPYRIGHT 1998 IFI
AN 2691693 IFIPAT;IFIUDB;IFICDB
TI ENDOTHELIN ANTAGONISTS INCORPORATING A CYCLOBUTANE; CARDIOVASCULAR DISORDERS; HYPOTENSIVE, ANTIISCHEMIC,ANTISHOCK, ANTIINFLAMMATORY, ANTIALLERGEN AGENTS
INF Rivero, Ralph A, Tinton Falls, NJ
Veber, Daniel F, Ambler, PA
Williams, Peter D, Harleysville, PA
IN Rivero Ralph A; Veber Daniel F; Williams Peter D
PAF Merck & Co, Inc, Rahway, NJ
PA Merck & Co Inc (54136)
EXNAM Ivy, C Warren
EXNAM Covington, Raymond
AG Camara, Valerie J
Daniel, Mark R
PI US 5492917 960220
AI US 93-128937 930929
FI US 5492917 960220
DT UTILITY
FS CHEMICAL
MRN 7717 MFN: 0535
CLMN 15
AB Novel compounds of the general structural formula I:

D R A W I N G

have endothelin antagonist activity and are therefore useful in treating cardiovascular disorders, such as hypertension, pulmonary hypertension, postischemic renal failure, vasospasm, cerebral and cardiac ischemia, myocardial infarction, endotoxic shock, inflammatory diseases including Raynaud's disease and asthma.

L23 ANSWER 7 OF 19 IFICDB COPYRIGHT 1998 IFI
AN 2666853 IFIPAT;IFIUDB;IFICDB
TI METHODS OF USING ALPHA-PHOSPHONOSULFONATE SQUALENE SYNTHETASE INHIBITORS INCLUDING THE TREATMENT OF ATHEROSCLEROSIS AND HYPERCHOLESTEROLEMIA
INF Biller, Scott A, Ewing, NJ
Dickson, Jr, John K, Mount Holly, NJ
Lawrence, R Michael, Yardley, PA
Magnin, David R, Hamilton, NJ
Sulsky, Richard B, Franklin Park, NJ
IN Biller Scott A; Dickson John K Jr; Lawrence R Michael; Magnin David R; Sulsky Richard B
PAF Bristol-Myers Squibb Company, Princeton, NJ
PA Bristol-Myers Squibb Co (22921)
EXNAM Richter, Johann
EXNAM Ambrose, Michael G
AG Rodney, Burton
PI US 5470845 951128
AI US 94-266843 940705
RLI US 92-967904 921028 CONTINUATION-IN-PART ABANDONED

US 93-109762 930820 DIVISION ABANDONED
FI US 5470845 951128
DT UTILITY
FS CHEMICAL
CLMN 14
AB Alpha -Phosphonosulfonate compounds are provided which inhibit the enzyme squalene synthetase and thereby inhibit cholesterol biosynthesis. These compounds have the formula

D R A W I N G

wherein R2 is OR5 or R5a; R3 and R5 are independently H, alkyl, arylalkyl, aryl or cycloalkyl; R5a is H, alkyl, arylalkyl or aryl; R4 is H, alkyl, aryl, arylalkyl, or cycloalkyl;, Z is H, halogen, lower alkyl or lower alkenyl; and R1 is a lipophilic group which contains at least 7 carbons and is alkyl, alkenyl, alkynyl, mixed alkenyl-alkynyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl; as further defined above; including pharmaceutically acceptable salts and or prodrug esters of the phosphonic (phosphinic) and/or sulfonic acids.

L23 ANSWER 8 OF 19 IFICDB COPYRIGHT 1998 IFI
AN 2565899 IFIPAT;IFIUDB;IFICDB
TI GUANIDINO COMPOUNDS AS REGULATORS OF **NITRIC OXIDE SYNTHASE**; VASCULAR SYSTEM DISORDERS
INF Gorsky, Lee D, Highland Park, IL
Kerwin, James F, Grayslake, IL
Murad, Ferid, Lake Forest, IL
IN Gorsky Lee D; Kerwin James F; Murad Ferid
PAF Abbott Laboratories, Abbott Park, IL
PA Abbott Laboratories (152)
EXNAM Henley, III, Raymond J
EXNAM MacMillan, Keith
AG Elder, Richard A
Gorman, Jr, Edward H
McNeil, James D
PI US 5380945 950110 (CITED IN 001 LATER PATENTS)
AI US 93-159972 931130
RLI US 89-369364 890621 CONTINUATION-IN-PART ABANDONED
US 91-755398 910905 CONTINUATION-IN-PART 5288897
FI US 5380945 950110
US 5288897
DT UTILITY
FS CHEMICAL
OS CA 124:8246
MRN 7072 MFN: 0623
CLMN 6
AB Compounds of the formula:

D R A W I N G

useful as regulators of **nitric oxide synthase** that indirectly modulate cyclic guanosine monophosphate (cGMP), pharmaceutical compositions thereof, for treating disorders of vascular smooth muscles, macrophages, neurons, platelets, bronchial smooth muscles, optic muscles and gastrointestinal smooth muscles, sickle cell anemia and diabetes.

L23 ANSWER 9 OF 19 IFICDB COPYRIGHT 1998 IFI
AN 2558867 IFIPAT;IFIUDB;IFICDB
TI 9-SUBSTITUTED CARBACYCLIN DERIVATIVES, PROCESSES FOR THEIR PREPARATION, AND THEIR USE AS MEDICINAL AGENTS; ANTICOGULANTS,

VASODILATING TO LOWER BLOOD PRESSURE, ANTISECRETORY AGENTS, CHEMICAL LINKAGE TO POLYMERIC CARRIERS OR PROTEINS TO PRODUCE ANTIBODIES
INF Klar, Ulrich, Berlin, DE
Nieuweboer, Bob, Berlin, DE
Sturzebecher, Claus-Steffen, Berlin, DE
Vorbruggen, Helmut, Berlin, DE
IN Klar Ulrich (DE); Nieuweboer Bob (DE); Sturzebecher Claus-Steffen (DE); Vorbruggen Helmut (DE)
PAF Schering Aktiengesellschaft, Berlin and Bergkamen, DE
PA Schering AG DE (13811)
EXNAM Brust, Joseph Paul
AG Millen, White, Zelano, & Branigan
PI US 5374654 941220
AI US 93-49649 930421
RLI US 91-688137 910419 CONTINUATION ABANDONED
US 89-332845 890322 CONTINUATION-IN-PART 5053400
PRAI DE 87-3725031 870724
FI US 5374654 941220
US 5053400
DT UTILITY
FS CHEMICAL
CLMN 10
AB The invention relates to carbacyclin derivatives of Formula I

D R A W I N G

wherein the various substituents are defined herein, including, inter alia, if R2 is a hydrogen atom, their salts with physiologically compatible bases, their cyclodextrin clathrates, and their use as medicinal agents.

L23 ANSWER 10 OF 19 IFICDB COPYRIGHT 1998 IFI
AN 2550006 IFIPAT;IFIUDB;IFICDB
TI CONTROLLED RELEASE DRUG DISPERSION DELIVERY DEVICE; HAVING COMPRESSED CORE OF DRUG AND POLYMER WHICH FORMS A GELATIN UPON HYDRATION AND A WATER INSOLUBLE, WATER IMPERMEABLE POLYMERIC COATING
INF Pipkin, James D, Lawrence, KS
Rork, Gerald S, Lawrence, KS
IN Pipkin James D; Rork Gerald S
PAF Merck & Co, Inc, Rahway, NJ
PA Merck & Co Inc (54136)
EXNAM Phelan, D Gabrielle
AG Bigley, Francis P
Daniel, Mark R
DiPrima, Joseph F
PI US 5366738 941122 (CITED IN 002 LATER PATENTS)
AI US 93-118836 930908
RLI US 82-902188 820729 CONTINUATION ABANDONED
US 91-815304 911227 CONTINUATION-IN-PART ABANDONED
FI US 5366738 941122
DT UTILITY
FS CHEMICAL
OS CA 122:89497
MRN 7095 MFN: 0092
CLMN 18
GI 7 Drawing Sheet; 7 Figures;
AB A device for the controlled delivery of a beneficial agent as a gelatinous dispersion consisting of (i) a core which contains a beneficial agent, a polymer which forms gelatinous microscopic particles upon hydration and if desired an agent to modulate the hydration of the polymer; and (ii) an impermeable, insoluble

coating which adheres to and surrounds the core and contains apertures which provide an area for the hydration and release of a dispersion comprising gelatinous microscopic particles.

L23 ANSWER 11 OF 19 IFICDB COPYRIGHT 1998 IFI
AN 2424534 IFIPAT;IFIUDB;IFICDB
TI PURIFICATION AND MOLECULAR CLONING OF **NITRIC OXIDE SYNTHASE**; DNA MOLECULE
INF Bredt, David S, Baltimore, MD
Snyder, Solomon H, Baltimore, MD
IN Bredt David S; Snyder Solomon H
PAF The Johns Hopkins University, Baltimore, MD
PA Johns Hopkins University (39884)
EXNAM Wax, Robert A
EXNAM Moore, William W
AG Banner, Birch, McKie & Beckett
PI US 5268465 931207 (CITED IN 002 LATER PATENTS)
AI US 91-642002 910118
FI US 5268465 931207
DT UTILITY
FS CHEMICAL
OS CA 120:184669
GOVI This invention was made with government support under grants MH18501 and DA-00074 awarded by the United States Public Health Service and the Department of Health and Human Services. The government has certain rights in the invention.
MRN 5629 MFN: 0112
CLMN 11
GI 3 Drawing Sheet; 3 Figures;
AB A method of purifying calmodulin-dependent **nitric oxide synthase** provides a homogeneous preparation of the enzyme. The enzyme is used to raise antibodies which are a useful immunohistochemical reagent. The antibodies localize calmodulin-dependent **nitric oxide synthase** to a number of anatomical sites, including retina, intestine, adrenal gland, and vasculature. However, activated macrophages, which are known to possess a nitric oxide producing activity, do not display an immunoreactive protein of appropriate size on Western blots using the antibodies. Nucleotide sequences encoding calmodulin-dependent **nitric oxide synthase** indicate a novel sequence with a flavin binding site consensus sequence.

L23 ANSWER 12 OF 19 IFICDB COPYRIGHT 1998 IFI
AN 2373938 IFIPAT;IFIUDB;IFICDB
TI BIOSYNTHETIC PRODUCTION OF 7-(1',2',6',7',8',8A'(R)-HEXAHYDRO-2'(S),6'(R)-DIMETHYL-8'(S)-HYDROXY-1'(S)-NAPHTHYL)-3(R),5(R)-DIHYDROXYHEPTANOIC ACID (TRIOL ACID)
INF Cianciosi, Steven J, Harrisonburg, VA
Conder, Michael J, Harrisonburg, VA
Cover, William H, Lansdale, PA
Dabora, Rebecca L, Andover, MA
Pisk, Eric T, Harrisonburg, VA
Stieber, Robert W, Harrisonburg, VA
Tehlewitz, Bogdan, McGaheysville, VA
Tewalt, Gregory L, Shenandoah, VA
IN Cianciosi Steven J; Conder Michael J; Cover William H; Dabora Rebecca L; Pisk Eric T; Stieber Robert W; Tehlewitz Bogdan; Tewalt Gregory L
PAF Merck & Co, Inc, Rahway, NJ
PA Merck & Co Inc (54136)
EXNAM Robinson, Douglas W
EXNAM Lankford, L Blaine

AG Caruso, Charles M
Dolan, Catherine A
Winokur, Melvin
PI US 5223415 930629 (CITED IN 002 LATER PATENTS)
AI US 92-832545 920207
RLI US 90-597643 901015 CONTINUATION ABANDONED
US 91-788691 911106 CONTINUATION-IN-PART ABANDONED
FI US 5223415 930629
DT UTILITY
FS CHEMICAL
OS CA 120:268337
MRN 6164 MFN: 0062
CLMN 26
AB Biosynthetic production of 7-(1',2',6',-7',8',8a'(R)-hexahydro2'(S),6'(R)-dimethyl-8'(S)-hydroxy-1'(S)-naphthyl)-3(R),5(R)dihydroxyheptanoic acid, ''triol acid'', is accomplished by enzymatic hydrolysis of **lovastatin** acid or a salt thereof, by treating it with Clonostachys compactiuscula ATCC 38009 or ATCC 74178, or mutants thereof, or a cell-free extract derived therefrom, or a hydrolase derived therefrom. The triol acid and its lactone form are both inhibitors of HMG-CoA reductase and thus useful as anti-hypercholesterolemic agents, and may also serve as intermediates for preparation of other HMG-CoA reductase inhibitors. Also, in the synthesis of **simvastatin** by direct methylation of **lovastatin**, selective hydrolysis of residual **lovastatin** salt by treatment with Clonostachys compactiuscula ATCC 38009 or ATCC 74178 or mutants thereof or a cell-free extract derived therefrom, or a hydrolase derived therefrom yields the ''triol'' salt which can be easily separated from **simvastatin**.

L23 ANSWER 13 OF 19 IFICDB COPYRIGHT 1998 IFI
AN 2213033 IFIPAT;IFIUDB;IFICDB
TI PROSTAGLANDINS; THROMBOXANE A2 ANTAGONIST
INF Jones, Robert L, Edinburgh, GB
Wilson, Norman H, Edinburgh, GB
IN Jones Robert L (GB); Wilson Norman H (GB)
PAF National Research Development Corporation, London, GB
PA National Research Development Corp GB (58315)
EXNAM Gerstl, Robert
AG Nixon & Vanderhye
PI US 5077309 911231 (CITED IN 001 LATER PATENTS)
AI US 90-501358 900328
PRAI GB 861018 860116
GB 86997 860116
FI US 5077309 911231
DT UTILITY; REASSIGNED; EXPIRED
FS CHEMICAL
MRN 5741 MFN: 0869
CLMN 37
AB Novel compounds have the formula (I)

D R A W I N G

where

D R A W I N G

represents one of the divalent cyclic groups

D R A W I N G

the letters a and b indicating in each case the points of

attachment of the substituents R1 and CV(R2)-NV'R, respectively; R1 is a group -(CH2)b-(A)a-(CH2)c-B-CH2-CO2R' in which A and B are each separately oxygen or sulphur, a is 0, b is 0 and c is an integer from 3 to 10, or a is 1, b is 0 or an integer from 1 to 7 and c is an integer from 2 to 9 with the sum of b and c being from 2 to 9, and CO2R' is a carboxy group or an amide, ester or salt derivative thereof; V and V' either each separately is hydrogen or together are the second bond of a carbon-nitrogen double bond; R2 is hydrogen, an aliphatic hydrocarbon group or an aliphatic hydrocarbon group substituted by an aromatic group directly or through an oxygen or sulphur atom; and R is a group OR3, -OR4, -D-R3, -N= R5 or -NW.G.W' in which D is -NH, -NH,CS-, -NH.CO-, -NH.CO.CH2N(R6)-, -NH.SO2-, -NH.CO.NH-, -NH.CS.NH-, NH.CO.O- or -NH.CS.O-, G is -CO- or -CS- and W and W' together are a group -(CH2)d- in which d is 3, 4, or 5, R3 is an aliphatic hydrocarbon group, an aromatic group or an aliphatic hydrocarbon group substituted by one or more aromatic groups directly or through an oxygen or sulphur atom, R4 is an aliphatic hydrocarbon group which is substituted through an oxygen atom by an aliphatic hydrocarbon group which is itself substituted directly by one or more aromatic groups, R5 is an aliphatic hydrocarbon group, and aromatic group in which the pi -electron system is not fully delocalized over the entire ring system, or aliphatic hydrocarbon group substituted by one or more aromatic groups directly or through an oxygen or sulphur atom, and R6 is hydrogen, an aliphatic hydrocarbon group, an aromatic group or an aliphatic hydrocarbon group substituted by one or more aromatic groups directly or through an oxygen or sulphur atom. The compounds are of value for use in pharmaceutical compositions particularly in the context of the inhibition of thromboxane activity.

L23 ANSWER 14 OF 19 IFICDB COPYRIGHT 1998 IFI
AN 2135246 IFIPAT;IFIUDB;IFICDB
TI PROSTAGLANDINS; THROMBORANE INHIBITOR
INF Jones, Robert L, Edinburgh, GB
Wilson, Norman H, Edinburgh, GB
IN Jones Robert L (GB); Wilson Norman H (GB)
PAF National Research Development Corporation, London, GB
PA National Research Development Corp GB (58315)
EXNAM Gerstl, Robert
AG Nixon & Vanderhye
PI US 5006539 910409 (CITED IN 002 LATER PATENTS)
AI US 89-319052 890306
RLI US 83-531899 830823 DIVISION 4628061
US 86-869735 860722 DIVISION 4837234
PRAI GB 8138715 811223
FI US 5006539 910409
US 4628061
US 4837234
DT UTILITY; REASSIGNED; EXPIRED
FS CHEMICAL
CLMN 37
AB Novel compounds have a formula (I)

D R A W I N G

wherein

D R A W I N G

represents a bicyclo (2,2,1) hept-2Z-ene, bicyclo (2,2, 1)heptane, 7-oxa-bicyclo (2,2,1) hept-2Z-ene, 7-oxa-bicyclo (2,2, 1) heptane, bicyclo (2,2,2) oct-2Z-ene or bicyclo (2,2,2) octane substituted at

the 5-position by the group R1 and at the 6position by the group ANR2R, a 6,6-dimethyl-bicyclo (3,1,1) heptane substituted at the 2-position by the group R1 and at the 3-position by the group ANR2R or at the 2-position by the group ANR2R and at the 3-position by the group R1, a cyclohex-1-ene or cyclohexane substituted at the 4-position by the group R1 and at the 5-position by the group ANR2R or a 1-hydroxyclopentane substituted at the 2-position by the group R1 and at the 2position by the group ANR2R, R1 is a 6-carboxyhex-2-enyl group or a modification thereof as defined herein; A is an unbranched or branched aliphatic hydrocarbon group with a chain length between the points of attachment to the divalent cyclic group and to the group NR2R of 1 to 5 carbon atoms or such a group substituted by an aromatic group; R2 is hydrogen, an aliphatic hydrocarbon group, an aromatic group or an aliphatic hydrocarbon group substituted by an aromatic group or groups; and R is a group CO.NR3R4, -CS.NR3R4, -CNH.NR3R4, -CO.R4 or -CO.R4 in which R3 is hydrogen, an aliphatic hydrocarbon group, an aromatic group or an aliphatic hydrocarbon group substituted by an aromatic group or groups, and R4 is an aliphatic hydrocarbon group, an aromatic group or an aliphatic hydrocarbon group substituted directly by an aromatic group or groups and/or through an oxygen or sulphur atom either by an aromatic group or by an aliphatic hydrocarbon group substituted directly by an aromatic group or groups. The compounds are of value for use in pharmaceutical compositions particularly in the context of the inhibition of thromboxane activity.

L23 ANSWER 15 OF 19 IFICDB COPYRIGHT 1998 IFI
AN 2089197 IFIPAT;IFIUDB;IFICDB
TI CYCLOPROPYL AZA PROSTAGLANDIN ANALOGS; THROMBOXANE ANTAGONIST
INF Floyd, David M, Pennington, NJ
Hall, Steven E, Ewing Township, Mercer County, NJ
Misra, Raj N, Hopewell, NJ
IN Floyd David M; Hall Steven E; Misra Raj N
PAF E R Squibb & Sons, Inc, Princeton, NJ
PA Squibb, E R & Sons Inc (79248)
EXNAM Shippen, Michael L
AG Furman, Jr, Theodore R
PI US 4965279 901023 (CITED IN 002 LATER PATENTS)
AI US 88-272953 881118
FI US 4965279 901023
DT UTILITY
FS CHEMICAL
OS CA 114:121850
MRN 5399 MFN: 0591
CLMN 13
AB Novel cyclopropyl aza prostaglandin analogs are disclosed having the formula

D R A W I N G

wherein A can be carbonyl, sulfonyl or a single bond. These compounds are useful, for example, as thromboxane antagonists.

L23 ANSWER 16 OF 19 IFICDB COPYRIGHT 1998 IFI
AN 1979023 IFIPAT;IFIUDB;IFICDB
TI NITRO ALIPHATIC COMPOUNDS, PROCESS FOR PREPARATION THEREOF AND USE THEREOF; ANTICOAGULANTS, HYPOTENSIVE AGENTS
INF Imanaka, Hiroshi, Osaka, JP
Iwami, Morita, Takarazuka, JP
Konsaka, Masanobu, Sakai, JP
Okamoto, Masanori, Osaka, JP
Takase, Shigehiro, Nishinomiya, JP

Uchida, Itsuo, Kyoto, JP
Umehara, Kazuyoshi, Ashiya, JP
IN IMANAKA HIROSHI (JP); IWAMI MORITA (JP); KONSAKA MASANOBU (JP); OKAMOTO MASANORI (JP); TAKASE SHIGEHIRO (JP); UCHIDA ITSUO (JP); UMEHARA KAZUYOSHI (JP)
PAF Fujisawa Pharmaceutical Co, Ltd, Osaka, JP
PA FUJISAWA PHARMACEUTICAL CO LTD JP (32600)
EXNAM Shaver, Paul F
AG Oblon, Spivak, McClelland, Maier & Neustadt
PI US 4863926 890905 (CITED IN 001 LATER PATENTS)
AI US 87-119091 871110
DCD 30 Aug 2005
RLI US 83-559260 831208 DIVISION 4767768
US 85-786754 851011 DIVISION 4778804
PRAI GB 8237068 821231
FI US 4863926 890905
US 4767768
US 4778804
DT UTILITY
FS CHEMICAL
CLMN 12
AB New nitro aliphatic compounds useful as antithrombotic and antihypertensing agents are disclosed.

L23 ANSWER 17 OF 19 IFICDB COPYRIGHT 1998 IFI
AN 1876560 IFIPAT;IFIUDB;IFICDB
TI NITRO ALIPHATIC COMPOUNDS, PROCESS FOR PREPARATION THEREOF AND USE THEREOF; ANTITHROMBIC, HYPOTENSIVE; OXIME-SUBSTITUTED
INF Imanaka, Hiroshi, Osaka, JP
Iwami, Morita, Takarazuka, JP
Kohsaka, Masanobu, Sakai, JP
Okamoto, Masanori, Osaka, JP
Takase, Shigehiro, Nishinomiya, JP
Uchida, Itsuo, Kyoto, JP
Umehara, Kazuyoshi, Ashiya, JP
IN IMANAKA HIROSHI (JP); IWAMI MORITA (JP); KOHSAKA MASANOBU (JP); OKAMOTO MASANORI (JP); TAKASE SHIGEHIRO (JP); UCHIDA ITSUO (JP); UMEHARA KAZUYOSHI (JP)
PAF Fujisawa Pharmaceutical Co, Ltd, Osaka, JP
PA FUJISAWA PHARMACEUTICAL CO LTD JP (32600)
EXNAM Shaver, Paul F
AG Oblon, Fisher, Spivak, McClelland & Maier
PI US 4767768 880830 (CITED IN 002 LATER PATENTS)
AI US 83-559260 831208
PRAI GB 8237068 821231
FI US 4767768 880830
DT UTILITY
FS CHEMICAL
MRN 4683 MFN: 0902
4683 0904
CLMN 14
AB New Nitro aliphatic compounds and their pharmaceutically acceptable salts are disclosed.

L23 ANSWER 18 OF 19 IFICDB COPYRIGHT 1998 IFI
AN 1584053 IFIPAT;IFIUDB;IFICDB
TI PROCESS FOR PREPARING INDOLES; AROMATIZATION HYPOTENSIVE AGENTS, VASODILATION
INF Sakai, Makiko, Kanagawa, JP
IN SAKAI MAKIKO (JP)
PAF Shionogi & Co, Ltd, Osaka, JP
PA SHIONOGI & CO LTD JP (76416)
EXNAM Bond, Robert T

AG Wenderoth, Lind & Ponack
PI US 4506079 850319 (CITED IN 001 LATER PATENTS)
AI US 80-127521 800305
PRAI JP 79-27010 7927010 790307
JP 80-10399 8010399 800130
FI US 4506079 850319
DT UTILITY
FS CHEMICAL
CLMN 10
AB Convenient intermediates for preparing 3-substituted-2hydroxypropyl aryl ether Beta -blockers, a reaction to the intermediates of the following formula and a conversion to obtain the said Beta -blockers are disclosed.

2-(Y-CH2-),6-P,7-Q,8-R,X-1,4-DIOXASPIRO(4,5)DECANE WHERE A DOTTED LINE JOINS C'S **NOS**. 6,7,8,9 AND 10

(wherein X is hydrogen or halogen; Y is halogen, hydroxy, lower acyloxy, amino, lower alkylamino, lower aralkylamino, lower acylamino, di-lower alkylamino, lower alkyleneamino, N-lower alkyl-N-lower aralkylamino, di-lower acylamino, N-lower alkyl-N-lower acylamino or N-tri-lower alkylsilylamino; one of P and R combined together with Q represents lower alkylene or alkenylene optionally interrupted by O, N or S and optionally substituted by lower alkyl, lower aralkyl, lower carboxylic acyl, carboxy, protected carboxy; hydroxy, lower alkoxy, lower acyloxy, oxo; amino, lower alkylamino, lower acylamino, nitro, nitroso, lower alkylthio, lower sulfonic acyl or halogen; and the remaining R or P is hydrogen or halogen; and dotted line represents the presence of one or two double bonds).

L23 ANSWER 19 OF 19 IFICDB COPYRIGHT 1998 IFI
AN 1198152 IFIPAT;IFIUDB;IFICDB
TI N-(3-PHENOXY-2-HYDROXY-PROPYL)-N-(2-PHENYL-2-HYDROXY-ETHYL)-AMINES; CARDIOTONIC, VASODILATION, HYPOTENSIVE, ANTIARRYTHMIA AGENTS
INF Koppe, Herbert, Ingelheim am Rhein, DE
Mentrup, Anton, Mainz-Kastel, DE
Reichl, Richard, Ingelheim am Rhein, DE
Renth, Ernst-Otto, Ingelheim am Rhein, DE
Schromm, Kurt, Ingelheim am Rhein, DE
IN KOPPE HERBERT (DE); MENTRUP ANTON (DE); REICHL RICHARD (DE); RENTH ERNST-OTTO (DE); SCHROMM KURT (DE)
PAF Boehringer Ingelheim GmbH, Ingelheim am Rhein, DE
PA BOEHRINGER INGELHEIM KG DE (10192)
EXNAM Torrence, Dolph H
AG Hammond & Littell
PI US 4146638 790327 (CITED IN 023 LATER PATENTS)
AI US 78-905593 780515
RLI US 77-768487 770214 CONTINUATION-IN-PART ABANDONED
PRAI DE 76-2606140 760217
FI US 4146638 790327
BE 851503
DE 2606140
FR 2341557
GB 1544883
NL 7701613
DT UTILITY
FS CHEMICAL
OS CA 87:201062
CLMN 6
AB Compounds of the formula

D R A W I N G

wherein R1 is halogen, hydroxyl, amino, alkyl, alkoxy or acylamido, R2 is hydrogen, hydroxyl, alkyl, alkoxy or carboxamido, R3 is hydrogen, halogen, alkyl or alkoxy, R4 is hydrogen, methyl or ethyl, and R5 and R6 are each hydrogen, halogen, alkyl, alkoxy, benzyloxy, hydroxyl, amino, cyano, carboxyl, carbalkoxy, carboxamido, alkylenecarboxamido or acylamido, PROVIDED, HOWEVER, THAT, WHEN R1 is 4-hydroxyl or 4-chloro, R2 and R3 are hydrogen, R4 is methyl and R5 is halogen or 2-halo, R6 is other than 4-hydroxyl or 4-benzyloxy; and nontoxic, pharmacologically acceptable acid addition salts thereof. The compounds as well as their salts are useful as cardiotonics, vasodilators, hypotensives and antiarrhythmics.

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     (FILE 'HOME' ENTERED AT 10:23:20 ON 28 JAN 1998)

     FILE 'IFICDB' ENTERED AT 10:23:30 ON 28 JAN 1998
L1          2482 S 05860/UN
L2          1435 S 05858/UN
L3           389 S 08423/UN
L4          1098 S NITRIC OXIDE SYNTHASE OR (NOS)
L5          1955 S ARGININE
L6            95 S (LOVASTATIN OR PRAVASTATIN OR SIMVASTATIN OR FLUVASTATI
L7           157 S 514565000/NCL
L8           247 S 514564000/NCL
L9           356 S L8 OR L7
L10            7 S L1 AND L4
L11           29 S L1 AND L5
L12            4 S L5 AND L6
L13           46 S L4 AND L5
L14            0 S L6 AND L13
L15            2 S L13 AND L1
L16           11 S L10 OR L12 OR L15
L17         2828 S L9 OR L1
L18           10 S L9 AND L1
L19           23 S L4 AND L9
L20           86 S L5 AND L9
L21            0 S L6 AND L20
L22           19 S L4 AND L20
L23           19 S L16 OR L18
L24           36 S L22 OR L23

=> d l22 1-19 bib,ab


L22  ANSWER 1 OF 19  IFICDB  COPYRIGHT 1998 IFI
AN    2881942  IFIPAT;IFIUDB;IFICDB
TI    METHOD FOR TREATING ANXIETY; NITRIC OXIDE
    SYNTHASE INHIBITOR
INF   Dunn, Robert W., P.O. Box 894, Old Lyme, CT, 06371
      La Marca, Suzanne, Cliffwood Beach, NJ
IN    Dunn Robert W; La Marca Suzanne
PAF   Dunn, Robert W., Warren, NJ
PA    Unassigned Or Assigned To Individual (68000)
EXNAM Geist, Gary
EXNAM Williams, Rosalynd
AG    Watov & Kipnes, P.C.
PI    US  5665757  970909
AI    US  94-274596  940713
FI    US  5665757  970909
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DT UTILITY
FS CHEMICAL
CLMN 6
AB A method of treating anxiety in a warm blooded animal by administering an anti-anxiety effective amount of a **nitric oxide synthase** inhibitor, and compositions containing the same.

L22 ANSWER 2 OF 19 IFICDB COPYRIGHT 1998 IFI
AN 2866564 IFIPAT;IFIUDB;IFICDB
TI POTENTIATION OF BIOREDUCTIVE AGENTS; ADMINISTERING NITROIMIDAZOLE DERIVATIVE **NITRIC OXIDE SYNTHASE** INHIBITOR; ANTITUMOR AGENTS
INF Adams, Gerald Edward, Didcot, GB
Stratford, Ian James, Didcot, GB
Wood, Pauline Joy, Didcot, GB
IN Adams Gerald Edward (GB); Stratford Ian James (GB); Wood Pauline Joy (GB)
PAF British Technology Group Limited, London, GB2
PA British Technology Group Ltd GB (30249)
EXNAM Goldberg, Jerome D
AG Nixon & Vanderhye
PI US 5652255 970729
AI US 94-235315 940429
PRAI GB 944400 940307
FI US 5652255 970729
DT UTILITY
FS CHEMICAL
CLMN 17
GI 3 Drawing Sheet; 7 Figures;
AB A human or animal subject having a solid tumour is treated by administering to the subject therapeutically effective amounts of a nitric oxide (NO) synthase inhibitor and a compound which is an imidazole or 1,2,4-triazole derivative of formula (A)

D R A W I N G

wherein X is selected from the group consisting of

D R A W I N G

wherein R is hydrogen or a C1-C6 alkyl group; each of R'1 to R'5 is independently selected from the group consisting of hydrogen, C1-C6 alkyl, hydroxy(C1-C6 alkyl), phenyl, (C1-C6 alkyl)phenyl and phenyl(C1-C6 alkyl); m is 0 or 1; n is 1 or 2; and Z' represents a leaving group which has the potential for expulsion via an intramolecular cyclisation reaction and which is not negatively-charged; or a physiologically acceptable acid addition salt thereof.

L22 ANSWER 3 OF 19 IFICDB COPYRIGHT 1998 IFI
AN 2832160 IFIPAT;IFIUDB;IFICDB
TI METHOD FOR TREATING EMESIS; ADMINISTERING **NITRIC OXIDE SYNTHASE** INHIBITOR
INF Dunn, Robert W, PO Box 894, Old Lyme, CT, 06371
Gregory, Robert L, New Providence, NJ
IN Dunn Robert W; Gregory Robert L
PAF Dunn, Robert W, Old Lyme, CT
PA Unassigned Or Assigned To Individual (68000)
EXNAM Cintins, Marianne M
EXNAM Moezie, M
AG Watov & Kipnes, PC
PI US 5621004 970415

AI US 94-253467 940603
FI US 5621004 970415
DT UTILITY
FS CHEMICAL
CLMN 7
AB A method of treating emesis in a warm blooded animal by administering an anti-emesis effective amount of a **nitric oxide synthase** inhibitor and compositions containing the same.

L22 ANSWER 4 OF 19 IFICDB COPYRIGHT 1998 IFI
AN 2812338 IFIPAT;IFIUDB;IFICDB
TI TREATMENT OF CENTRAL NERVOUS SYSTEM DISORDERS ASSOCIATED WITH PSYCHOTIC BEHAVIOR AND DEMENTIA WITH A COMBINATION OF NEUROLEPTIC DRUGS AND TAURINE, OR DERIVATIVES THEREOF, TO PREVENT THE DEVELOPMENT OF TARDIVE DYSKINESIA; TREATMENT OF SCHIZOPHRENIA WITH REDUCED SIDE EFFECTS
INF Lidsky, Theodore I, Atlantic Highlands, NJ
IN Lidsky Theodore I
PAF Research Foundation for Mental Hygiene, Inc, Albany, NY
PA Research Foundation for Mental Hygiene Inc (11651)
EXNAM Henley, III, Raymond
AG Morgan & Finnegan, LLP
PI US 5602150 970211
AI US 95-440824 950515
RLI US 92-956109 921002 CONTINUATION ABANDONED
FI US 5602150 970211
DT UTILITY
FS CHEMICAL
MRN 7536 MFN: 0754
CLMN 34
GI 6 Drawing Sheet; 12 Figures;
AB The present invention relates to a method of treatment and a composition used to prevent the development of the adverse manifestation of tardive dyskinesia in individuals suffering from mental illness such as schizophrenia and undergoing treatment with neuroleptic or antipsychotic agents. The experimentallybased rationale for the present invention indicates that conventional neuroleptic drugs induce tardive dyskinesia because they evoke a glutamate afflux whose excitotoxic action is unopposed by other properties of these drugs, including dopamine receptor blockade. The present invention provides effective drug therapies for schizophrenia comprising conventional neuroleptics or antipsychotic drugs given in combination with taurine, a taurine precursor such as hypotaurine, taurine derivatives, or compounds similar in action to taurine, to render benign tardive dyskinesia as an adverse effect. The combined administration of any of the conventional neuroleptics with taurine and the like offers the benefits of a safe and effective treatment that is generally affordable and vastly improves upon the limited, existing drug treatments which frequently exert crippling and long-lasting side effects unless drug is withdrawn.

L22 ANSWER 5 OF 19 IFICDB COPYRIGHT 1998 IFI
AN 2760168 IFIPAT;IFIUDB;IFICDB
TI METHODS FOR IMPROVING THERAPEUTIC EFFECTIVENESS OF AGENTS FOR THE TREATMENT OF SOLID TUMORS AND OTHER DISORDERS; ADMINISTERING **NITRIC OXIDE SYNTHASE** INHIBITOR AND HYPOXIC CYTOTOXIN
INF Bonaventura, Joseph, Beaufort, NC
Dewhirst, Mark W, Chapel Hill, NC
DeAngelo, Joseph, Hamtramck, MI
Meyer, Robert E, Cary, NC

IN Bonaventura Joseph; Dewhirst Mark W; DeAngelo Joseph; Meyer Robert E
PAF Apex Bioscience, Inc, Durham, NC
Duke University, Durham, NC
North Carolina State University, Raleigh, NC
PA Apex Bioscience Inc (6982)
Duke University (25202)
North Carolina State University at Raleigh (37796)
EXNAM Ramsuer, Robert W
EXNAM Peabody, John
AG Pennie & Edmonds
PI US 5554638 960910
AI US 94-246882 940520
RLI US 93-66756 930524 CONTINUATION-IN-PART
FI US 5554638 960910
DT UTILITY
FS CHEMICAL
OS CA 125:293021
MRN 7231 MFN: 0595
7231 0598
7231 0600
CLMN 24
GI 14 Drawing Sheet; 14 Figures;
AB The present invention is directed to the use of an inhibitor of NO activity, such as a nitric oxide scavenger or an NO synthase inhibitor, as an antitumor therapy to reduce tumor blood flow and oxygenation. The invention is also directed to administration of a nitric oxide scavenger or a **nitric oxide synthase** inhibitor to enhance the effectiveness of tumor therapy with hypoxic or acidic chemotherapeutic agents or hyperthermia. The invention is also directed to the administration of a **nitric oxide synthase** substrate to a subject previously administered a **nitric oxide synthase** inhibitor, in order to selectively inhibit tumor perfusion. In a specific example, administration of cell free hemoglobin, a nitric oxide scavenger, in conjunction with mitomycin C, a hypoxic cytotoxin, results in a significant delay in tumor growth of a human tumor xenograft in a mouse compared to mitomycin C alone. In another example, the administration of an inhibitor of **nitric oxide synthase** followed by the administration of a substrate of the enzyme causes a specific irreversible reduction of tumor blood flow, while normal blood flow is restored.

L22 ANSWER 6 OF 19 IFICDB COPYRIGHT 1998 IFI
AN 2750233 IFIPAT;IFIUDB;IFICDB
TI PREVENTING CONVERSION OF CITRULLINE TO ARGININOSUCCINATE TO LIMIT PATHOLOGICAL NITRIC OXIDE OVERPRODUCTION; HYPOTENSIVE THERAPY
INF Griffith, Owen W, Milwaukee, WI
Gross, Steven S, New York, NY
IN Griffith Owen W; Gross Steven S
PAF The Medical College of Wisconsin Research Foundation, Inc, Milwaukee, WI
PA Medical College of Wisconsin The (5187)
EXNAM Jordan, Kimberly
PI US 5545625 960813
AI US 94-354585 941212
FI US 5545625 960813
DT UTILITY; REASSIGNED
FS CHEMICAL
CLMN 35
GI 5 Drawing Sheet; 5 Figures;
AB Administration of argininosuccinate synthetase activity reducing

agents, e.g., argininosuccinate synthetase induction blocking agents (e.g., antibiotics that bind to DNA sequences present in the upstream regulatory region of the argininosuccinate synthetase gene, such as mithramycin) and argininosuccinate synthetase inhibitors (e.g., L-citrulline antagonists such as methyl citrulline and L-aspartate antagonists such as Daspartate) is useful to prevent or treat sepsis or cytokineinduced systemic hypotension, is useful in the treatment of sepsis or cytokine-induced systemic hypotension to restore vascular sensitivity to the effects of Alpha 1-adrenergic agonists, and is useful to suppress an immune response, e.g., in treating inflammation. In one embodiment, certain argininosuccinate synthetase activity reducing agents are used together with **arginine** antagonists to treat sepsis or cytokine induced hypotension.

L22 ANSWER 7 OF 19 IFICDB COPYRIGHT 1998 IFI
AN 2750222 IFIPAT;IFIUDB;IFICDB
TI CONTROLLING NITROGEN OXIDE CONCENTRATIONS TO MODULATE SKELETAL MUSCLE CONTRACTION; USING A NITRIC ACID SYNTHASE INHIBITOR OR NITRIC OXIDE SCAVENGER
INF Kobzik, Lester, Needham, MA
Stamler, Jonathan, Chapel Hill, NC
IN Kobzik Lester; Stamler Jonathan
PAF Duke Univ, Durham, NC
Harvard College, Cambridge, MA
PA Duke University (542)
Harvard College, President & Fellows of (25202)
EXNAM Russel, Jeffrey E
AG Herron, Charles J
Olstein, Elliot M
PI US 5545614 960813
AI US 94-349436 941205
RLI US 94-276105 940715 CONTINUATION-IN-PART
FI US 5545614 960813
DT UTILITY; REASSIGNED
FS CHEMICAL
OS CA 125:212705
CLMN 7
GI 5 Drawing Sheet; 8 Figures;
AB A method for inhibiting or relaxing skeletal muscle contractions and for treating disease states resulting from or exacerbated by undesirable skeletal muscle contractions by administering a skeletal muscle relaxing amount of nitroxyl ion(NO-), nitrosonium ion(NO+), nitric oxide and nitric oxide adducts or providers. A process for stimulating, improving or enhancing muscle contraction in a mammal by treating the mammal with an effective amount of (i) a **nitric oxide synthase** inhibitor or (ii) a nitric oxide scavenger.

L22 ANSWER 8 OF 19 IFICDB COPYRIGHT 1998 IFI
AN 2747811 IFIPAT;IFIUDB;IFICDB
TI METHOD AND FORMULATION OF STIMULATING NITRIC OXIDE SYNTHESIS; ADMINISTERING MIXTURE OF **ARGININE** AND VENOUS DILATOR UNTIL DESIRABLE STATE OF VASORELAXATION IS OBTAINED
INF Kaesemeyer, W H, 2433 McDowell St, August, GA, 30904
IN Kaesemeyer W H
PAF Unassigned
PA Unassigned Or Assigned To Individual (68000)
EXNAM Killos, Paul J
AG Pearne, Gordon, McCoy & Granger
PI US 5543430 960806
AI US 94-321051 941005

FI US 5543430 960806
DT UTILITY
FS CHEMICAL
CLMN 22
GI 5 Drawing Sheet; 5 Figures;
AB A therapeutic mixture comprising a mixture of L-**arginine** and an agonist of **nitric oxide synthase**, namely nitroglycerin, is disclosed for the treatment of diseases related to vasoconstriction, wherein the vasoconstriction is relieved by stimulating the constitutive form of **nitric oxide synthase** (cNOS) to produce native nitric oxide (NO). The native NO having superior beneficial effect when compared to exogenous NO produced by a L-**arginine** independent pathway in terms of the ability to reduce clinical endpoints and mortality.

L22 ANSWER 9 OF 19 IFICDB COPYRIGHT 1998 IFI
AN 2730531 IFIPAT;IFIUDB;IFICDB
TI METHOD OF TREATING SCHIZOPHRENIA, TOURETTE'S SYNDROME, MANIA, AUTISM, AND OBSESSIVE COMPULSIVE DISORDER WITH INHIBITORS OF BRAIN **NITRIC OXIDE SYNTHASE**; ADMINISTERING HYPODOMAMINERGIC AGENTS, SELECTED FROM NITRO-L-**ARGININE**, N-IMINO ETHYL-L-ORNITHINE, L-CANAVANINE AND N-MONOMETHYL-L-**ARGININE**
INF Freeman, Bobby L, Little Rock, AR
Karson, Craig N, Little Rock, AR
Lyon, Melvin, Little Rock, AR
IN Freeman Bobby L; Karson Craig N; Lyon Melvin
PAF University of Arkansas, Little Rock, AR
PA Arkansas, University of (5221)
EXNAM Henley, III, Raymond
EXNAM Jarvis, William R A
AG Adler, Benjamin Aaron
PI US 5527825 960618
AI US 94-223776 940406
FI US 5527825 960618
DT UTILITY
FS CHEMICAL
MRN 6958 MFN: 0943
CLMN 9
GI 3 Drawing Sheet; 7 Figures;
AB The present invention provides a pharmaceutical compositions suitable for the treatment of brain diseases characterized by excessive activity of brain dopamine systems and/or nitric oxide systems. Also provided is a method of treating psychiatric and neurologic diseases.

L22 ANSWER 10 OF 19 IFICDB COPYRIGHT 1998 IFI
AN 2666855 IFIPAT;IFIUDB;IFICDB
TI OVULATION CONTROL BY REGULATING NITRIC OXIDE LEVELS WITH **ARGININE** DERIVATIVES; CONTRACEPTIVES BY INHIBITING OVULATION
INF Garfield, Robert E, Friendswood, TX
Yallampalli, Chandrasekhar, Houston, TX
IN Garfield Robert E; Yallampalli Chandrasekhar
PAF Board of Regents, the University of Texas System, Austin, TX
PA Texas, University of System (83960)
EXNAM Criares, Theodore J
AG Arnold, White & Durkee
PI US 5470847 951128
AI US 93-165309 931210
FI US 5470847 951128
DT UTILITY

FS CHEMICAL
MRN 6850 MFN: 0923
CLMN 19
GI 1 Drawing Sheet; 1 Figures;
AB Inhibition of ovulation in a female may be achieved by administering an **arginine** derivative which acts as a nitric oxide sythase inhibitor, alone or in combination with one or more of a progestin, an estrogen, and an LH-RH antagonist, thereby preventing conception.

L22 ANSWER 11 OF 19 IFICDB COPYRIGHT 1998 IFI
AN 2660133 IFIPAT;IFIUDB;IFICDB
TI HEME BINDING COMPOUNDS AND USE THEREOF; HYPOTENSIVE
INF Griffith, Owen W, Milwaukee, WI
Narayanan, Krishnaswamy, Wauwatosa, WI
IN Griffith Owen W; Narayanan Krishnaswamy
PAF The Medical College of Wisconsin Research Foundation, Inc, Milwaukee, WI
PA Medical College of Wisconsin The (5187)
EXNAM Raymond, Richard L
EXNAM Lambkin, Deborah
PI US 5464858 951107 (CITED IN 001 LATER PATENTS)
AI US 94-354257 941212
RLI US 93-87371 930707 CONTINUATION 5424447
FI US 5464858 951107
US 5424447
DT UTILITY
FS CHEMICAL
CLMN 7
GI 5 Drawing Sheet; 5 Figures;
AB Inhibitors of nitric oxide formation from **arginine** useful for treating hypotension, inflammation, stroke and to restore vascular contractile sensitivity to the effects of Alpha 1 adrenergic agonists are physiologically active compounds including N delta -substituted ornithine or N Epsilon substituted lysine moieties or monoalkyl carbon-substituted N delta -substituted ornithine or N Epsilon -substituted lysine moieties, having the formula

D R A W I N G

wherein R is (CH2)yCH3 or H, R' is CH2 or C(H)(CH2)yCH3, and R'' is CH2 or C(H)(CH2)yCH3, with y ranging from 0 to 5, and x is 0 or 1 and wherein none or only one of R, R' and R'' provides an alkyl substituent on ornithine or lysine moiety, and wherein Q is a heme binding moiety and/or a sulfur-containing binding moiety and Q' is -NH2 when there is a double bond between the omega carbon and Q and Q' is =NH when there is a single bond between the omega carbon and Q, and physiologically acceptable acid addition salts thereof.

L22 ANSWER 12 OF 19 IFICDB COPYRIGHT 1998 IFI
AN 2647316 IFIPAT;IFIUDB;IFICDB
TI SUBSTITUTED ARGININES AND SUBSTITUTED HOMOARGININES AND USE THEREOF; ENZYME INHIBITORS AND HYPERTENSIVE AGENTS
INF Griffith, Owen W, Milwaukee, WI
IN Griffith Owen W
PAF Cornell Research Foundation, Inc, Ithaca, NY
PA Cornell Research Foundation Inc (20656)
EXNAM Shippen, Michael L
PI US 5453441 950926
AI US 94-328956 941024
DCD 25 Jan 2011
RLI US 92-889345 920528 CONTINUATION 5281627

US 93-147306 931105 CONTINUATION ABANDONED
FI US 5453441 950926
US 5281627
DT UTILITY
FS CHEMICAL
GOVI This invention was made at least in part with Government support under Grant DK 37116 from National Institutes of Health.
CLMN 14
GI 2 Drawing Sheet; 2 Figures;
AB Guanidino substituted arginines or homoarginines based on monoalkyl carbon-substituted ornithines or lysines, having the formula

D R A W I N G

wherein R is (CH2)yCH3 or H, R' is CH2 or C(H)(CH2)yCH3, and R'' is CH2 or C(H)(CH2)yCH3, with y ranging from 0 to 5, and x is 0 or 1 and Q is an alkyl group containing from 1 to 6 carbon atoms or NH2 or NO2, and only one of R, R' and R'' providing an alkyl substituent on the ornithine or lysine moiety. Preferred compounds are Alpha -methyl-N omega -methyl-DL-**arginine**, RSBeta -methyl-N omega -methyl-DL-**arginine**, RS- gamma -methyl-N omega -methyl-DL-**arginine**, Alpha -methyl-N omega -amino-DLarginine, RS- Beta -methyl-N omega -amino-DL-**arginine**, RS- gamma -methyl-N omega -amino-DL-**arginine**, Alpha -methyl-N omega nitro-DL-**arginine**, RS- Beta -methyl-N omega -nitro-DL-**arginine**, and RS-gamma -methyl-N omega -nitro-DL-**arginine**. A composition includes said compound together with a pharmaceutically acceptable carrier. Methods of use are directed to delivering said compound to inducible **nitric oxide synthase** to inhibit the ability of the enzyme to catalyze the conversion of **arginine** to nitric oxide, to administering said compound to inhibit pathological overproduction of nitric oxide from **arginine** and to administering said compound to a subject having systemic hypotension due to the pathological overproduction of nitric oxide and an Alpha 1 adrenergic agonist to increase blood pressure in the subject to a clinically acceptable level.

L22 ANSWER 13 OF 19 IFICDB COPYRIGHT 1998 IFI
AN 2643125 IFIPAT;IFIUDB;IFICDB
TI METHOD OF TREATING CHRONIC INFLAMMATORY DISEASES; **NITRIC OXIDE SYNTHASE** INHIBITOR OR SCAVENGER
INF Allen, Janice B, Angier, NC
McCartney-Francis, Nancy L, Gaithersburg, MD
Wahl, Sharon M, Gaithersburg, MD
IN Allen Janice B; McCartney-Francis Nancy L; Wahl Sharon M
PAF The United States of America as represented by the Department of Health and Human Services, Washington, DC
PA U S of America Health & Human Services (6814)
EXNAM Cintins, Marianne M
EXNAM Jarvis, William R A
AG National Institutes of Health
PI US 5449688 950912 (CITED IN 001 LATER PATENTS)
AI US 93-39849 930330
FI US 5449688 950912
DT UTILITY
FS CHEMICAL
OS CA 123:246828
MRN 6547 MFN: 0150
CLMN 11
GI 8 Drawing Sheet; 17 Figures;
AB The present invention provides a method for treating chronic inflammatory conditions, including autoimmune diseases by

administering an effective amount of an agent, such as a **nitric oxide synthase** inhibitor, a nitric oxide scavenger, or an inhibitor of tetrahydrobiopterin synthesis, to decrease the amount of nitric oxide present at the site of inflammation.

L22 ANSWER 14 OF 19 IFICDB COPYRIGHT 1998 IFI
AN 2634442 IFIPAT;IFIUDB;IFICDB
TI THERAPEUTICS FOR MANAGEMENT OF COCAINE INDUCED TOXICITY; ADMINISTERING **NITRIC OXIDE SYNTHASE** INHIBITOR
INF Itzhak, Yossef, 9407 SW 151st Ave, Miami, FL, 33196
IN Itzhak Yossef
PAF Unassigned
PA Unassigned Or Assigned To Individual (68000)
EXNAM Cintins, Marianne M
EXNAM Moezie, M
AG Blum, Alvin S
PI US 5441982 950815
AI US 93-125808 930924
FI US 5441982 950815
DT UTILITY
FS CHEMICAL
OS CA 123:218439
CLMN 6
GI 1 Drawing Sheet; 2 Figures;
AB Repetitive administrations of cocaine over a period of days causes the animal body to become more sensitive to the drug. A dose of cocaine that was not toxic to a novice user may be toxic or even lethal to an habituated user. These toxic effects include craving, seizures, brain ischemia and death. The mechanism of action of these toxic effects appears to be through the glutamatergic neurotransmitter system as evidenced by blocking with antagonists for N-methyl-D-aspartate receptors. However, these antagonists have undersirable side effects. Applicant demonstrates that the toxic effects of repetitive cocaine administrations can be reversed by the administration of inhibitors of the enzyme **nitric oxide synthase** which is also involved in the neurotransmitter system. The drugs which inhibit the enzyme **nitric oxide synthase** include N-nitro-L-**arginine** and N-nitro-L-**arginine** methyl ester. The method of treatment with these drugs includes administration in various forms by various routes.

L22 ANSWER 15 OF 19 IFICDB COPYRIGHT 1998 IFI
AN 2632153 IFIPAT;IFIUDB;IFICDB
TI TREATMENTS FOR MALE SEXUAL DYSFUNCTION; TREATING PRIAPISM BY APPLYING TO ERECT PENIS AN INHIBITOR OF NO SYNTHETASE TO CAUSE PENIS TO BECOME FLACCID
INF Bredt, David S, Baltimore, MD
Burnett, Arthur L, Baltimore, MD
Chang, Thomas S K, Baltimore, MD
Lowenstein, Charles J, Tacoma Park, MD
Snyder, Solomon H, Baltimore, MD
IN Bredt David S; Burnett Arthur L; Chang Thomas S K; Lowenstein Charles J; Snyder Solomon H
PAF The Johns Hopkins University, Baltimore, MD
PA Johns Hopkins University (39884)
EXNAM Henley, III, Raymond
AG Banner, Birch, McKie & Beckett
PI US 5439938 950808 (CITED IN 001 LATER PATENTS)
AI US 93-43821 930407
FI US 5439938 950808

DT UTILITY
FS CHEMICAL
OS CA 123:188641
MRN 6528 MFN: 0635
CLMN 33
GI 1 Drawing Sheet; 6 Figures;
AB Methods and devices are taught for regulating penile erection and urethral function. Inhibitors of **nitric oxide synthase** and precursors of nitric oxide are applied to relax or contract the muscles of the corpus cavernosum and the urethra.

L22 ANSWER 16 OF 19 IFICDB COPYRIGHT 1998 IFI
AN 2571605 IFIPAT;IFIUDB;IFICDB
TI TREATMENT OF STROKE WITH NITRIC-OXIDE RELEASING COMPOUNDS
INF Moskowitz, Michael A, Belmont, MA
IN Moskowitz Michael A
PAF The General Hospital Corporation, Boston, MA
PA General Hospital Corp The (10301)
EXNAM Henley, III, Raymond J
AG Wolf, Greenfield & Sacks
PI US 5385940 950131
AI US 92-972267 921105
FI US 5385940 950131
DT UTILITY
FS CHEMICAL
OS CA 122:151385
GOVI Studies were supported by NINCDS #NS10828 to the MGH Interdepartmental Stroke Program Project (MAM).
MRN 6313 MFN: 0271
CLMN 4
GI 3 Drawing Sheet; 4 Figures;
AB A method for treatment of stroke in a patient, involving administering to the patient a nitric oxide-releasing compound. A preferred compound of the invention is L-**arginine**.

L22 ANSWER 17 OF 19 IFICDB COPYRIGHT 1998 IFI
AN 2558864 IFIPAT;IFIUDB;IFICDB
TI METHODS AND COMPOSITIONS FOR THE TREATMENT OF HYPOTENSION WITH **ARGININE** FREE ESSENTIAL AND NONESSENTIAL AMINO ACIDS AND **ARGININE** DERIVATIVES; HYPERTENSIVE AGENTS; INHIBIT NITRIC OXIDE PRODUCTION
INF Griffith, Owen W, Milwaukee, WI
Gross, Steven S, New York, NY
Kilbourn, Robert G, Houston, TX
IN Griffith Owen W; Gross Steven S; Kilbourn Robert G
PAF Board of Regents, The University of Texas System, Austin, TX
PA Texas, University of System (83960)
EXNAM Cintins, Marianne M
EXNAM Criapres, T J
AG Arnold, White & Durkee
PI US 5374651 941220
AI US 92-902653 920623
RLI US 91-767265 910927 CONTINUATION-IN-PART 5286739
FI US 5374651 941220
US 5286739
DT UTILITY
FS CHEMICAL
OS CA 122:96516
GOVI The government has rights in the present invention as research relevant to the development thereof was funded by NIH grant #DK37116.
MRN 6255 MFN: 0709

6255 0713
CLMN 46
GI 7 Drawing Sheet; 12 Figures;
AB Methods and compositions for treating and inhibiting hypotension are provided. A therapeutic regimen useful in the present invention includes an **arginine**-free parenteral formulation administered concurrently with or followed by an **arginine** analog. The combination therapy provides an augmentation of the antihypotensive effect found by the present inventors with **arginine** analogs, such as N omega -methyl-L-**arginine**, N omega -amino-Larginine or N omega -nitro-L-**arginine**. These **arginine** analogs, otherwise described as **nitric oxide synthase** inhibitors, provide for a decrease in nitric oxide concentrations, and are demonstrated to elicit an increase in blood pressure in vivo, particularly in animals with cytokine and/or endotoxin induced hypotension. The parenteral formulation of the therapeutic regimen and methods of the invention are **arginine**-free and provide a decrease in plasma **arginine** levels. Reduced plasma and tissue levels of **arginine** in the animal function to augment the hypertensive action of **arginine** analogs to be administered concurrently or subsequent to administration of the parenteral formulation. This method provides a regiment for treating and/or inhibiting hypotension attendant a variety of conditions, including chemotherapeutic agent therapy (i.e., IFN, TNF), septic shock, trauma, exposure to endotoxins or cytokines, or other condition in which hypotension is attendant. The **arginine**-free formulations may also include ornithine, citrulline, or both.

L22 ANSWER 18 OF 19 IFICDB COPYRIGHT 1998 IFI
AN 2439410 IFIPAT;IFIUDB;IFICDB
TI SUBSTITUTED ARGININES AND SUBSTITUTED HOMOARGININES AND USE THEREOF; GUANIDINE SUBSTITUTED ARGININES
INF Griffith, Owen W, Milwaukee, WI
IN Griffith Owen W
PAF Cornell Research Foundation, Inc, Ithaca, NY
PA Cornell Research Foundation Inc (20656)
EXNAM Shippen, Michael L
PI US 5281627 940125 (CITED IN 007 LATER PATENTS)
AI US 92-889345 920528
FI US 5281627 940125
DT UTILITY
FS CHEMICAL
GOVI This invention was made at least in part with Government support under Grant DK 37116 from National Institutes of Health.
MRN 6165 MFN: 0684
CLMN 4
GI 2 Drawing Sheet; 2 Figures;
AB Guanidino substituted arginines or homoarginines based on monoalkyl carbon-substituted ornithines or lysines, having the formula

D R A W I N G

wherein R is (CH2)yCH3 or H, R' is CH2 or C(H)(CH2)yCH3, and R'' is CH2 or C(H)(CH2)yCH3, with y ranging from 0 to 5, and x is 0 or 1 and Q is an alkyl group containing from 1 to 6 carbon atoms or NH2 or NO2, and only one of R, R' and R'' providing an alkyl substituent on the ornithine or lysine moiety. Preferred compounds are Alpha -methyl-N omega -methyl-DL-**arginine**, RSBeta -methyl-N omega -methyl-DL-**arginine**, RS- gamma -methyl-N omega -methyl-DL-**arginine**, Alpha -methyl-N omega -amino-DLarginine, RS- Beta -methyl-N omega -amino-DL-

arginine, RS- gamma -methyl-N omega -amino-DL-
arginine, Alpha -methyl-N omega nitro-DL-**arginine**
, RS- Beta -methyl-N omega -nitro-DL-**arginine**, and RS-
gamma -methyl-N omega -nitro-DL-**arginine**. A composition
includes said compound together with a pharmaceutically acceptable
carrier. Methods of use are directed to delivering said compound to
inducible **nitric oxide synthase** to
inhibit the ability of the enzyme to catalyze the conversion of
arginine to nitric oxide, to administering said compound to
inhibit pathological overproduction of nitric oxide from
arginine and to administering said compound to a subject
having systemic hypotension due to the pathological overproduction
of nitric oxide and an Alpha 1 adrenergic agonist to increase
blood pressure in the subject to a clinically acceptable level.

L22 ANSWER 19 OF 19 IFICDB COPYRIGHT 1998 IFI
AN 2430675 IFIPAT;IFIUDB;IFICDB
TI N6-(HYDRAZINOIMINOMETHYL)LYSINE AND METHOD OF INHIBITING NITRIC OXIDE FORMATION IN BODY
INF Griffith, Owen W, New York, NY
IN Griffith Owen W
PAF Cornell Research Foundation, Inc, Ithaca, NY
PA Cornell Research Foundation Inc (20656)
EXNAM Robinson, Douglas W
EXNAM Hung, Deborah L
PI US 5273875 931228 (CITED IN 004 LATER PATENTS)
AI US 92-865060 920408
RLI US 91-673831 910322 DIVISION 5132453
FI US 5273875 931228
US 5132453
DT UTILITY
FS CHEMICAL
GOVI This invention was made at least in part with Government support under National Institutes of Health grant number DK 37116. The Government has certain rights in the invention.
CLMN 1
GI 3 Drawing Sheet; 3 Figures;
AB Physiologically active N6-(hydrazinoiminomethyl)lysine or pharmaceutically acceptable acid addition salt thereof is administered in a nitric oxide synthesis inhibiting amount to a subject in need of such inhibition (e.g., a subject with low blood pressure, e.g., due to sepsis or to therapeutic administration of cytokines, or needing immunosuppressive effect) or is added to a medium containing isolated organs, intact cells, cell homogenates or tissue homogenates in an amount sufficient to inhibit nitric oxide formation to elucide or control the biosynthesis, metabolism or physiological role of nitric oxide. Compared to known nitric oxide synthesis inhibitors, N6(hydrazinoiminomethyl)lysine and its acid addition salts show a greater relative activity toward inducible isoform of **nitric oxide**
synthase than toward constitutive isoform of **nitric**
oxide synthase. N6-(hydrazinoiminomethyl)lysine
and its pharmaceutically acceptable acid addition salts are substantially less toxic than are NG-aminoarginine and its pharmaceutically acceptable acid addition salts.

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L1 2482 S 05860/UN

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L2          1435 S 05858/UN
L3           389 S 08423/UN
L4          1098 S NITRIC OXIDE SYNTHASE OR (NOS)
L5          1955 S ARGININE
L6            95 S (LOVASTATIN OR PRAVASTATIN OR SIMVASTATIN OR FLUVASTATI
L7           157 S 514565000/NCL
L8           247 S 514564000/NCL
L9           356 S L8 OR L7
L10            7 S L1 AND L4
L11           29 S L1 AND L5
L12            4 S L5 AND L6
L13           46 S L4 AND L5
L14            0 S L6 AND L13
L15            2 S L13 AND L1
L16           11 S L10 OR L12 OR L15
L17         2828 S L9 OR L1
L18           10 S L9 AND L1
L19           23 S L4 AND L9
L20           86 S L5 AND L9
L21            0 S L6 AND L20
L22           19 S L4 AND L20
L23           19 S L16 OR L18
L24           36 S L22 OR L23

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L24  ANSWER 1 OF 36  IFICDB  COPYRIGHT 1998 IFI
PI    US  5665757  970909

L24  ANSWER 2 OF 36  IFICDB  COPYRIGHT 1998 IFI
PI    US  5652255  970729

L24  ANSWER 3 OF 36  IFICDB  COPYRIGHT 1998 IFI
PI    US  5645839  970708

L24  ANSWER 4 OF 36  IFICDB  COPYRIGHT 1998 IFI
PI    US  5621004  970415

L24  ANSWER 5 OF 36  IFICDB  COPYRIGHT 1998 IFI
PI    US  5602150  970211

L24  ANSWER 6 OF 36  IFICDB  COPYRIGHT 1998 IFI
PI    US  5593876  970114

L24  ANSWER 7 OF 36  IFICDB  COPYRIGHT 1998 IFI
PI    US  5582838  961210

L24  ANSWER 8 OF 36  IFICDB  COPYRIGHT 1998 IFI
PI    US  5554638  960910

L24  ANSWER 9 OF 36  IFICDB  COPYRIGHT 1998 IFI
PI    US  5545625  960813

L24  ANSWER 10 OF 36  IFICDB  COPYRIGHT 1998 IFI
PI    US  5545614  960813

L24  ANSWER 11 OF 36  IFICDB  COPYRIGHT 1998 IFI
PI    US  5543430  960806

L24  ANSWER 12 OF 36  IFICDB  COPYRIGHT 1998 IFI
PI    US  5527825  960618
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L24 ANSWER 13 OF 36 IFICDB COPYRIGHT 1998 IFI
PI US 5492917 960220

L24 ANSWER 14 OF 36 IFICDB COPYRIGHT 1998 IFI
PI US 5470847 951128

L24 ANSWER 15 OF 36 IFICDB COPYRIGHT 1998 IFI
PI US 5470845 951128

L24 ANSWER 16 OF 36 IFICDB COPYRIGHT 1998 IFI
PI US 5464858 951107 (CITED IN 001 LATER PATENTS)

L24 ANSWER 17 OF 36 IFICDB COPYRIGHT 1998 IFI
PI US 5453441 950926

L24 ANSWER 18 OF 36 IFICDB COPYRIGHT 1998 IFI
PI US 5449688 950912 (CITED IN 001 LATER PATENTS)

L24 ANSWER 19 OF 36 IFICDB COPYRIGHT 1998 IFI
PI US 5441982 950815

L24 ANSWER 20 OF 36 IFICDB COPYRIGHT 1998 IFI
PI US 5439938 950808 (CITED IN 001 LATER PATENTS)

L24 ANSWER 21 OF 36 IFICDB COPYRIGHT 1998 IFI
PI US 5385940 950131

L24 ANSWER 22 OF 36 IFICDB COPYRIGHT 1998 IFI
PI US 5380945 950110 (CITED IN 001 LATER PATENTS)

L24 ANSWER 23 OF 36 IFICDB COPYRIGHT 1998 IFI
PI US 5374654 941220

L24 ANSWER 24 OF 36 IFICDB COPYRIGHT 1998 IFI
PI US 5374651 941220

L24 ANSWER 25 OF 36 IFICDB COPYRIGHT 1998 IFI
PI US 5366738 941122 (CITED IN 002 LATER PATENTS)

L24 ANSWER 26 OF 36 IFICDB COPYRIGHT 1998 IFI
PI US 5281627 940125 (CITED IN 007 LATER PATENTS)

L24 ANSWER 27 OF 36 IFICDB COPYRIGHT 1998 IFI
PI US 5273875 931228 (CITED IN 004 LATER PATENTS)

L24 ANSWER 28 OF 36 IFICDB COPYRIGHT 1998 IFI
PI US 5268465 931207 (CITED IN 002 LATER PATENTS)

L24 ANSWER 29 OF 36 IFICDB COPYRIGHT 1998 IFI
PI US 5223415 930629 (CITED IN 002 LATER PATENTS)

L24 ANSWER 30 OF 36 IFICDB COPYRIGHT 1998 IFI
PI US 5077309 911231 (CITED IN 001 LATER PATENTS)

L24 ANSWER 31 OF 36 IFICDB COPYRIGHT 1998 IFI
PI US 5006539 910409 (CITED IN 002 LATER PATENTS)

L24 ANSWER 32 OF 36 IFICDB COPYRIGHT 1998 IFI
PI US 4965279 901023 (CITED IN 002 LATER PATENTS)

L24 ANSWER 33 OF 36 IFICDB COPYRIGHT 1998 IFI
PI US 4863926 890905 (CITED IN 001 LATER PATENTS)

L24 ANSWER 34 OF 36 IFICDB COPYRIGHT 1998 IFI
PI US 4767768 880830 (CITED IN 002 LATER PATENTS)

L24 ANSWER 35 OF 36 IFICDB COPYRIGHT 1998 IFI
PI US 4506079 850319 (CITED IN 001 LATER PATENTS)

L24 ANSWER 36 OF 36 IFICDB COPYRIGHT 1998 IFI
PI US 4146638 790327 (CITED IN 023 LATER PATENTS)

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